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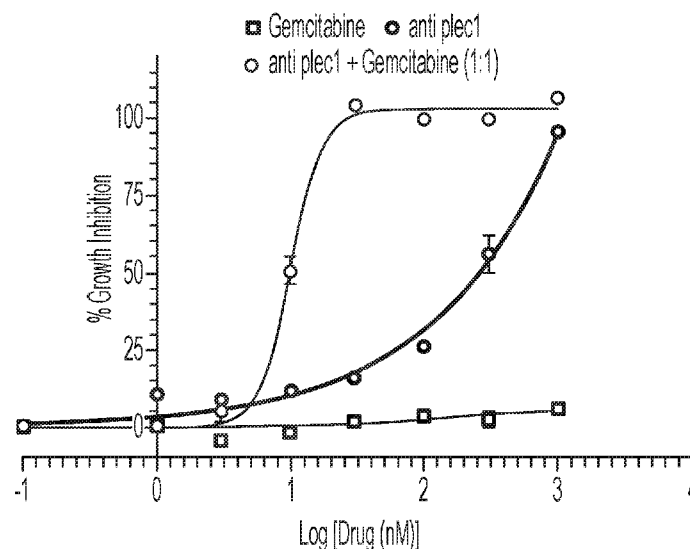


FIG. 3

(57) Abstract: Aspects of the disclosure provide compositions and methods for treating cancer characterized by surface expression of plectin-1. The disclosure relates, in part, to combinations of therapeutic agents (e.g., anti-plectin-1 antibodies and certain small molecules) that function together (e.g., synergistically) to inhibit cancer cell growth. In some embodiments, the disclosure relates to anti-plectin-1 antibody-drug-conjugates (ADCs).



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PLECTIN-1 BINDING ANTIBODIES AND USES THEREOF**RELATED APPLICATIONS**

This application claims the benefit under 35 U.S.C. 119(e) of the filing date of U.S. provisional Application Serial Number 62/571,246, filed October 11, 2017, entitled “PLECTIN-1 BINDING ANTIBODIES AND USES THEREOF”, the entire contents of which are incorporated herein by reference.

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer death in the United States showing a rapid clinical course leading to death. Once diagnosed, PDAC has a median survival of 6 months and a 5-year survival rate of only 3 percent (Li et al., *Lancet* 363:1049-1057 (2004)).

As chemotherapy and radiotherapy have only modest benefits, and surgery is only possible in 20% of patients, early detection that allows surgical resection offers the best hope for longer survival (Yeo et al., *Ann Surg* 222:580-588 (1995); discussion 588-592). Indeed, the detection and treatment of PDAC or high-grade precursors in high-risk patient groups (*e.g.*, hereditary cancer syndromes, chronic pancreatitis, and new-onset diabetes) represents a critical unmet need in the cancer diagnostic portfolio (Brentnall et al., *Ann. Intern. Med.* 131:247-255 (1999); Canto et al., *Clin. Gastroenterol. Hepatol.* 2:606-621 (2004)).

SUMMARY

In some aspects, the disclosure relates to compositions and methods useful for treating certain cancers (*e.g.*, pancreatic cancer, ovarian cancer, *etc.*). The disclosure is based, in part, on combinations of anti-plectin-1 antibodies and anti-cancer agents (*e.g.*, small molecules, such as gemcitabine, pyrrolbenzodiazepines (PBDs), *etc.*), administered as a single composition or separately, that act together (*e.g.*, synergistically) to inhibit cancer cell growth. In some embodiments, the combinations are formulated to produce an antibody-drug-conjugate (ADC).

Aspects of the disclosure are based on plectin-1 antibodies that specifically bind to plectin-1 exposed on the surface of a cell (*e.g.*, a cancer cell). Thus in some aspects, the disclosure provides a composition comprising: an antibody that specifically binds to plectin-1 exposed on the surface of a cancer cell; and one or more anti-cancer agents, wherein the antibody and the anticancer agents are not linked.

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In some aspects, the disclosure provides a composition comprising an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2 (*e.g.*, an amino acid sequence having at least 90%, at least 95%, at least 96%, at least 97% at least 98% or at least 99% identity to SEQ ID NO: 2); and an anti-cancer agent, wherein the antibody and the anti-cancer agent are not linked. In some embodiments, an anti-
5 plectin-1 antibody and the anti-cancer agent act synergistically (*e.g.*, as measured by the Chou-Talalay method).

In some embodiments, an antibody or antigen binding fragment comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 23 or SEQ ID NO: 67. In some
10 embodiments, an antibody or antigen binding fragment comprises a light chain variable region having a sequence set forth as: SEQ ID NO: 45 or SEQ ID NO: 89.

In some embodiments, an antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 23 and a light chain variable region having a sequence set forth as: SEQ ID NO: 45.

15 In some embodiments, an antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 67 and a light chain variable region having a sequence set forth as: SEQ ID NO: 89.

In some embodiments, an antibody or antigen binding fragment binds to cell-surface exposed plectin-1 (*e.g.*, plectin-1 expressed on the surface of a cell, for example a cancer cell).

20 In some embodiments, an anti-cancer agent is selected from the group consisting of Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Adrucil (Fluorouracil), Afinitor (Everolimus), Efudex (Fluorouracil), Erlotinib Hydrochloride, Everolimus, Fluoroplex (Fluorouracil), Fluorouracil, Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Mitomycin C, Mitozytrex (Mitomycin C), Mutamycin (Mitomycin C), Paclitaxel Albumin-
25 stabilized Nanoparticle Formulation, Sunitinib Malate, Sutent (Sunitinib Malate), and Tarceva (Erlotinib Hydrochloride), Altretamine, Alkeran (Melphalan), Avastin (Bevacizumab), Bevacizumab, Carboplatin, Clade (Cyclophosphamide), Cisplatin, Cyclophosphamide, Cytosan (Cyclophosphamide), Doxorubicin Hydrochloride, Dox-SL (Doxorubicin Hydrochloride Liposome), DOXIL (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride
30 Liposome, Evacet (Doxorubicin Hydrochloride Liposome), Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Hycamtin (Topotecan Hydrochloride), LipoDox (Doxorubicin Hydrochloride Liposome), Lynparza (Olaparib), Melphalan, Neosar (Cyclophosphamide),

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Niraparib Tosylate Monohydrate, Olaparib, Paclitaxel, Paraplat (Carboplatin), Paraplatin (Carboplatin), Platinol (Cisplatin), Platinol-AQ (Cisplatin), Rubraca (Rucaparib Camsylate), Rucaparib Camsylate, Taxol (Paclitaxel), Thiotepe, Topotecan Hydrochloride, and Zejula (Niraparib Tosylate Monohydrate). In some embodiments, the anti-cancer agent is gemcitabine (gem) or cisplatin.

In some aspects, the disclosure provides an antibody-drug-conjugate (ADC) comprising an antibody or antigen binding fragment that specifically binds to plectin-1 exposed on the surface of a cell (*e.g.*, a cancer cell) linked to one or more anti-cancer agent molecules (*e.g.*, between 2 and 100 anti-cancer agent molecules).

In some aspects, the disclosure provides an antibody-drug-conjugate (ADC) comprising an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2 (*e.g.*, an amino acid sequence having at least 90%, at least 95%, at least 96%, at least 97% at least 98% or at least 99% identity to SEQ ID NO: 2) linked to one or more anti-cancer agent molecules (*e.g.*, between 2 and 100 anti-cancer agent molecules).

In some embodiments, one or more anti-cancer agent molecules are directly linked to an antibody or antigen binding fragment.

In some embodiments, one or more anti-cancer agent molecules are indirectly linked to the antibody or antigen binding fragment via a linker, for example a photolinker or a flexible amino acid sequence linker.

In some embodiments, 2, 3, 4, or 5 anti-cancer agent molecules are linked to an antibody or antigen binding fragment.

In some embodiments, an anti-cancer agent molecule is auristatin or pyrrolobenzodiazepine (PBD). In some embodiments, a PBD molecule is a PBD dimer.

In some aspects, the disclosure provides a method for treating cancer, the method comprising administering to a subject having cancer an effective amount of an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2, and an anti-cancer agent. In some embodiments, the subject is a mammal, for example a human.

In some embodiments of methods described by the disclosure, an antibody or antigen binding fragment and an anti-cancer agent are administered together (*e.g.*, as a composition or ADC as described herein). In some embodiments, an antibody or antigen binding fragment and an anti-cancer agent are administered separately to a subject.

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In some embodiments, a cancer is characterized by expression of plectin-1 on the surface of the cancer cell. In some embodiments, a cancer is ovarian cancer, esophageal cancer, head and neck squamous cell carcinoma, or pancreatic cancer. In some embodiments, the pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC).

5 In some embodiments of methods described by the disclosure, an antibody, anti-cancer agent, ADC, or composition is administered at a dose in a range of 1 ng/kg and 100 mg/kg.

BRIEF DESCRIPTION OF DRAWINGS

FIGs. 1A-1B show representative data for affinity and specificity of an anti-plec1
10 antibody on human recombinant protein (FIG. 1A) and human (YapC and L3.6pl) and mouse (Han14.3) pancreatic cell lines (FIG. 1B).

FIGs. 2A-2C show treatment of YapC cells with anti-plec1 antibody. FIG. 2A shows treatment of cells with anti-plec1 results in G0 and G2 growth arrest. FIG. 2B shows representative data for EC50 of anti-plec1 for YapC cells. FIG. 2C shows the phenotypic effect
15 of anti-plec1 treatment on YapC microtubule (top, left to right) and actin microfilaments (bottom, left to right).

FIG. 3 shows a combination of anti-plec1 with gemcitabine (gem) has synergistic effects on cancer cells. Equal molar concentrations of anti-plec1 and gem were incubated with cells for 72 hrs. After incubation, cells were processed. Combination therapy resulted in a 20-fold
20 decrease in IC50.

DETAILED DESCRIPTION

The disclosure relates, in some aspects, to compositions and methods for treatment of certain cancers (*e.g.*, cancers characterized by surface expression of plectin-1). Plectin-1 is a useful biomarker for a variety of cancers, including ovarian, esophageal, and head and neck
25 squamous cells carcinomas, as well as pancreatic ductal adenocarcinoma. In contrast with antibody targets, such as CD30, which is targeted by Brentuximab vedotin, and Her2, which is targeted by Ado-trastuzumab Emtansine, plectin-1 is a particularly useful target because it is present on the cell surface exclusively in certain cancer cells (*e.g.*, pancreatic ductal adenocarcinoma cells, ovarian cancer cells, *etc.*), thus giving exquisite specificity and
30 selectivity. Accordingly, in some embodiments, the disclosure relates to antibodies and antigen binding fragments that bind specifically to plectin-1 on the surface of cancer cells, and methods

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of use thereof. In some embodiments, binding of an anti-plectin-1 antibody as described by the disclosure to a plectin-1 expressing cell induces death (*e.g.*, triggers apoptosis) of the cell.

The disclosure is based, in part, on the recognition that certain combinations of anti-plectin-1 antibodies and anti-cancer agents are capable of mediating enhanced inhibition of cancer cell growth when delivered together, either as separate compositions or as a single composition (*e.g.*, a composition comprising an anti-plectin-1 antibody and an anti-cancer agent, or an ADC as described herein).

Antibodies that Bind Plectin-1

The present disclosure provides compositions (*e.g.*, ADCs) comprising antibodies and antigen binding fragments that bind to plectin-1 on the surface of cancer cells. The monoclonal antibodies of the disclosure may be murine, humanized or chimeric or in other forms. A detailed description of the antibodies of the disclosure is provided herein.

Plectin-1 is a high molecular weight protein (500 kDa) that links intermediate filaments to microtubules and microfilaments, in addition to anchoring the cytoskeleton the plasma and nuclear membranes (reviewed in Sonnenberg, et al., *Exp Cell Res* 313:2189-2203 (2007)).

Generally, plectin-1 levels are low in normal pancreatic ductal cells but its expression is upregulated in cells having certain cancers (*e.g.*, precursor pancreatic intraepithelial neoplasia (PanINs), pancreatic ductal adenocarcinoma cells (PDACs), ovarian cancer cells, *etc.*). Plectin-1 exhibits distinct cytoplasm and nuclear localization in normal fibroblasts, whereas an aberrant expression on the cell membrane is observed in cells having certain cancers (*e.g.*, PDACs). Altered subcellular localization of plectin-1 has also been observed in an autoimmune condition, paraneoplastic pemphigus, and in the associated lymphoproliferative neoplasm, Castleman's disease (Aho *et al.*, *J Invest Dermatol* 113:422-423 (1999)). Plectin-1 also has important roles in signal transduction. Thus, plectin-1 in cells having certain cancers (*e.g.*, precursor pancreatic intraepithelial neoplasia (PanINs), pancreatic ductal adenocarcinoma cells (PDACs), ovarian cancer cells, *etc.*) may have an impact on signaling pathways that regulate cell migration, polarity and energy metabolism related to carcinogenesis. Accordingly, in some embodiments, the disclosure provides antibodies and antigen binding fragments that bind to plectin-1 on the surface of cancer cells.

In some embodiments, antibodies, also known as immunoglobulins, are tetrameric glycosylated proteins composed of two light (L) chains of approximately 25 kDa each and two

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heavy (H) chains of approximately 50 kDa each. Two types of light chain, termed lambda and kappa, may be found in antibodies. Depending on the amino acid sequence of the constant domain of heavy chains, immunoglobulins can be assigned to five major classes: A, D, E, G, and M, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂. Each light chain typically includes an N-terminal variable (V) domain (V_L) and a constant (C) domain (C_L). Each heavy chain typically includes an N-terminal V domain (V_H), three or four C domains (C_H1-3), and a hinge region. The C_H domain most proximal to V_H is designated as C_H1. The V_H and V_L domains consist of four regions of relatively conserved sequences called framework regions (FR1, FR2, FR3, and FR4), which form a scaffold for three regions of hypervariable sequences (complementarity determining regions, CDRs). The CDRs contain most of the residues responsible for specific interactions of the antibody with the antigen. CDRs are referred to as CDR1, CDR2, and CDR3. Accordingly, CDR constituents on the heavy chain are referred to as CDRH1, CDRH2, and CDRH3, while CDR constituents on the light chain are referred to as CDRL1, CDRL2, and CDRL3. The CDRs typically refer to the Kabat CDRs, as described in Sequences of Proteins of Immunological Interest, US Department of Health and Human Services (1991), eds. Kabat *et al.* Another standard for characterizing the antigen binding site is to refer to the hypervariable loops as described by Chothia. See, *e.g.*, Chothia, D. *et al.* (1992) *J. Mol. Biol.* 227:799-817; and Tomlinson *et al.* (1995) *EMBO J.* 14:4628-4638. Still another standard is the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, generally, *e.g.*, Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S, and Kontermann, R., Springer-Verlag, Heidelberg). Embodiments described with respect to Kabat CDRs can alternatively be implemented using similar described relationships with respect to Chothia hypervariable loops or to the AbM-defined loops, or combinations of any of these methods.

In some embodiments, anti-plectin-1 antibodies of the present disclosure and the nucleic acid molecules of the present disclosure that encode the antibodies include the CDR amino acid and nucleic acid sequences shown in Table 1 below.

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Table 1.

Antibody	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
Pab2						
Amino acid:	(SEQ ID NO: 17)	(SEQ ID NO: 19)	(SEQ ID NO: 21)	(SEQ ID NO: 39)	(SEQ ID NO: 41)	(SEQ ID NO: 43)
Nuc. Acid:	(SEQ ID NO: 6)	(SEQ ID NO: 8)	(SEQ ID NO: 10)	(SEQ ID NO: 28)	(SEQ ID NO: 30)	(SEQ ID NO: 32)
Pab1						
Amino acid:	(SEQ ID NO: 61)	(SEQ ID NO: 63)	(SEQ ID NO: 65)	(SEQ ID NO: 83)	(SEQ ID NO: 85)	(SEQ ID NO: 87)
Nuc. Acid:	(SEQ ID NO: 50)	(SEQ ID NO: 52)	(SEQ ID NO: 54)	(SEQ ID NO: 72)	(SEQ ID NO: 74)	(SEQ ID NO: 76)

In some embodiments, anti-plectin-1 binding agents (*e.g.*, anti-plectin-1 antibodies) of the disclosure include any antibody or antigen binding fragment that includes a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, or CDRL3, or combinations thereof, as provided for any one of the antibodies shown in Table 1. In some embodiments, anti-plectin-1 binding agents include the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of any one of the antibodies shown in Table 1. The disclosure also includes any nucleic acid sequence that encodes a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, or CDRL3 as provided for any one of the antibodies shown in Table 1. Antibody heavy and light chain CDR3 domains may play a particularly important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, the anti-plectin-1 antibodies of the disclosure, or the nucleic acid molecules thereof, may include at least the heavy and/or light chain CDR3s of antibodies as shown in Table 1 or as set forth by SEQ ID NOs: 14, 21, 23, 36, 43, 45, 58, 65, 67, 80, 87 or 89.

The complete amino acid and nucleic acid sequences for the heavy chain variable region and light chain variable region of the antibodies listed in Table 2.

Table 2.

Antibody	Heavy Chain Variable Region	Light Chain Variable Region
PAb2		
Amino acid:	SEQ ID NO: 23	SEQ ID NO: 45
Nuc. Acid:	SEQ ID NO: 12	SEQ ID NO: 34
PAb1		
Amino acid:	SEQ ID NO: 67	SEQ ID NO: 89
Nuc. Acid:	SEQ ID NO: 56	SEQ ID NO: 78

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In some embodiments, anti-plectin antibodies of the disclosure include any antibody that includes a heavy chain variable domain or a light chain variable domain or both as shown in Table 1, or as described in the sequence listing of this disclosure (*e.g.*, SEQ ID NOs: 14, 23, 36, 45, 58, 67, 80, or 89). The disclosure also includes any nucleic acid molecule encoding an antibody that includes a heavy chain variable domain or a light chain variable domain nucleic acid sequence, or both, as shown in Table 1 or as described in the sequence listing of this disclosure (*e.g.*, SEQ ID NOs: 3, 12, 25, 34, 47, 56, 69, or 78).

Anti-plectin-1 antibodies of this disclosure may optionally comprise antibody constant regions or parts thereof. For example, a V_L domain may be attached at its C-terminal end to a light chain constant domain like C_k or C_λ . Similarly, a V_H domain or portion thereof may be attached to all or part of a heavy chain like IgA, IgD, IgE, IgG, and IgM, and any isotype subclass. Antibodies may include suitable constant regions (see, for example, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, Md. (1991)). Therefore, antibodies within the scope of this disclosure include V_H and V_L domains, or an antigen binding portion thereof, combined with constant regions known in the art. In some embodiments, anti-plectin-1 antibodies of the disclosure comprise a heavy chain constant region comprising a sequence represented by SEQ ID NOs: 3, 13, 25, 35, 47, 57, 69, or 79.

In certain embodiments, the V_H and/or V_L domains may be reverted to germline sequence, *e.g.*, the FR of these domains are mutated using conventional molecular biology techniques to match those produced by the germline cells. In other embodiments, the FR sequences remain diverged from the consensus germline sequences.

In some embodiments, anti-plectin-1 antibodies or antigen binding fragments may or may not include the framework region of the antibodies, for example as set forth in SEQ ID NOs: 5, 7, 9, 11, 16, 18, 20, 22, 27, 29, 31, 33, 38, 40, 42, 44, 49, 51, 53, 55, 60, 62, 64, 66, 71, 73, 75, 77, 82, or 84. In some embodiments, anti-plectin-1 antibodies are murine antibodies. In some embodiments, anti-plectin-1 antibodies are chimeric or humanized antibodies.

It should be appreciated that, in some embodiments, the disclosure contemplates variants (*e.g.*, homologs) of amino acid and nucleic acid sequences for the heavy chain variable region and light chain variable region of the antibodies. "Homology" refers to the percent identity between two polynucleotides or two polypeptide moieties. The term "substantial homology", when referring to a nucleic acid, or fragment thereof, indicates that, when optimally aligned with

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appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in about 90 to 100% of the aligned sequences. For example, in some embodiments, nucleic acid sequences sharing substantial homology are at least 90%, at least 91%, at least 92% at least 93%, at least 94%, at least 95%, at least 96% at
5 least 97%, at least 98% at least 99% sequence identity. When referring to a polypeptide, or fragment thereof, the term "substantial homology" indicates that, when optimally aligned with appropriate gaps, insertions or deletions with another polypeptide, there is nucleotide sequence identity in about 90 to 100% of the aligned sequences. The term "highly conserved" means at least 80% identity, preferably at least 90% identity, and more preferably, over 97% identity. For
10 example, in some embodiments, highly conserved proteins share at least 85%, at least 90%, at least 91%, at least 92% at least 93%, at least 94%, at least 95%, at least 96% at least 97%, at least 98% at least 99% identity. In some cases, highly conserved may refer to 100% identity. Identity is readily determined by one of skill in the art by, for example, the use of algorithms and computer programs known by those of skill in the art.

15 In some embodiments, an anti-plectin-1 antibodies of the disclosure can bind to plectin-1 with high affinity, *e.g.*, with a K_d less than 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M or lower. For example, anti-plectin-1 antibodies or antigen binding fragments thereof can bind to plectin-1 with an affinity between 5 pM and 500 nM, *e.g.*, between 50 pM and 100 nM, *e.g.*, between 500 pM and 50 nM. The disclosure also includes antibodies or antigen binding fragments that
20 compete with any of the antibodies described herein for binding to plectin-1 and that have an affinity of 50 nM or lower (*e.g.*, 20 nM or lower, 10 nM or lower, 500 pM or lower, 50 pM or lower, or 5 pM or lower). The affinity and binding kinetics of the anti-plectin-1 antibody can be tested using any method known in the art including but not limited to biosensor technology (*e.g.*, OCTET or BIACORE).

25 As used herein, the term "antibody" generally refers to an immunoglobulin. All derivatives thereof which maintain or possess specific binding ability are also provided herein. An antibody preparation may be monoclonal or polyclonal.

As used herein, the term "antibody fragment" or "antigen binding fragment" refers to any derivative of an antibody which is less than full-length. Generally, an antigen binding fragment
30 retains at least a significant portion of the full-length antibody's specific binding ability. Examples of antigen binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, scFv, Fv, dsFv diabody, affibodies, and Fd fragments. Antigen binding fragments may be produced

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by any appropriate means. For instance, an antigen binding fragment may be enzymatically or chemically produced by fragmentation of an intact antibody or it may be recombinantly produced from a gene encoding the partial antibody sequence. Alternatively, an antigen binding fragment may be wholly or partially synthetically produced. An antigen binding fragment may optionally be a single chain antibody fragment. Alternatively, a fragment may comprise multiple chains which are linked together, for instance, by disulfide linkages. An antigen binding fragment may also optionally be a multimolecular complex. A functional antigen binding fragment will typically comprise at least about 50 amino acids and more typically will comprise at least about 200 amino acids.

Single-chain Fvs (scFvs) are recombinant antigen binding fragments consisting of only the variable light chain (VL) and variable heavy chain (VH) covalently connected to one another by a polypeptide linker. Either VL or VH may be the NH₂-terminal domain. The polypeptide linker may be of variable length and composition so long as the two variable domains are bridged without serious steric interference. Typically, the linkers are comprised primarily of stretches of glycine and serine residues with some glutamic acid or lysine residues interspersed for solubility.

Diabodies are dimeric scFvs. The components of diabodies typically have shorter peptide linkers than most scFvs, and they show a preference for associating as dimers.

A Fv fragment is an antigen binding fragment which consists of one VH and one VL domain held together by noncovalent interactions. The term dsFv is used herein to refer to an Fv with an engineered intermolecular disulfide bond to stabilize the VH-VL pair.

A F(ab')₂ fragment is an antigen binding fragment essentially equivalent to that obtained from immunoglobulins (typically IgG) by digestion with an enzyme pepsin at pH 4.0-4.5. The fragment may be recombinantly produced.

A Fab fragment is an antigen binding fragment essentially equivalent to that obtained by reduction of the disulfide bridge or bridges joining the two heavy chain pieces in the F(ab')₂ fragment. The Fab' fragment may be recombinantly produced.

A Fab fragment is an antigen binding fragment essentially equivalent to that obtained by digestion of immunoglobulins (typically IgG) with the enzyme papain. The Fab fragment may be recombinantly produced. The heavy chain segment of the Fab fragment is the Fd piece.

An affibody is a small protein comprising a three-helix bundle that functions as an antigen binding molecule (*e.g.*, an antibody mimetic). Generally, affibodies are approximately 58 amino

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acids in length and have a molar mass of approximately 6 kDa. Affibody molecules with unique binding properties are acquired by randomization of 13 amino acids located in two alpha-helices involved in the binding activity of the parent protein domain. Specific affibody molecules binding a desired target protein can be isolated from pools (libraries) containing billions of different variants, using methods such as phage display.

Antibody-drug conjugates (ADCs)

Some aspects of the disclosure relate to antibody-drug conjugates targeted against plectin-1. As used herein, “antibody drug conjugate” or “ADC” refers to molecules comprising an antibody, or antigen binding fragment thereof, linked to one or more targeted molecules (*e.g.*, a biologically active molecule, such as a therapeutic molecule, and/or a detectable label). Accordingly, in some embodiments, antibodies or antigen binding fragments of the disclosure may be modified with a therapeutic agent. As used herein, the term “therapeutic agent” refers to chemicals or drugs or proteins that are able to inhibit cell function, inhibit cell replication or kill mammalian cells, preferably human cells, more preferably human cancer cells. Examples of therapeutic agents include but are not limited to cytotoxic moieties, radioisotopes, molecules of plant, fungal, or bacterial origin (*e.g.*, plant-derived toxins (*e.g.*, secondary metabolites), glycosides, antimicrobial compounds (*e.g.*, streptomycin, penicillin, *etc.*), biological proteins (*e.g.*, protein toxins), particles (*e.g.*, recombinant viral particles, *e.g.*, via a viral coat protein)), or mixtures thereof. The therapeutic agent can be an intracellularly active drug or other agent, such as short-range radiation emitters, including, for example, short-range, high-energy alpha-emitters (*e.g.*, ^{131}I).

In some embodiments, a therapeutic agent is an anti-cancer agent. The term “anti-cancer agent” refers to chemicals or drugs or proteins that are able to inhibit cancer cell function, inhibit cancer cell growth or replication, or kill cancer cells. In some embodiments, an anti-cancer agent is a chemical or drug or protein that is approved by the U.S. Food and Drug Administration (FDA) for treatment of cancer. Examples of anti-cancer agents include but are not limited to Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Adrucil (Fluorouracil), Afinitor (Everolimus), Efudex (Fluorouracil), Erlotinib Hydrochloride, Everolimus, Fluoroplex (Fluorouracil), Fluorouracil, Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Mitomycin C, Mitozytrex (Mitomycin C), Mutamycin (Mitomycin C), Paclitaxel Albumin-stabilized Nanoparticle Formulation, Sunitinib Malate, Sutent (Sunitinib Malate), and Tarceva

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(Erlotinib Hydrochloride), Altretamine, Alkeran (Melphalan), Avastin (Bevacizumab), Bevacizumab, Carboplatin, Clade (Cyclophosphamide), Cisplatin, Cyclophosphamide, Cytosan (Cyclophosphamide), Doxorubicin Hydrochloride, Dox-SL (Doxorubicin Hydrochloride Liposome), DOXIL (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Evacet (Doxorubicin Hydrochloride Liposome), Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Hycamtin (Topotecan Hydrochloride), LipoDox (Doxorubicin Hydrochloride Liposome), Lynparza (Olaparib), Melphalan, Neosar (Cyclophosphamide), Niraparib Tosylate Monohydrate, Olaparib, Paclitaxel, Paraplat (Carboplatin), Paraplatin (Carboplatin), Platinol (Cisplatin), Platinol-AQ (Cisplatin), Rubraca (Rucaparib Camsylate), Rucaparib Camsylate, Taxol (Paclitaxel), Thiotepa, Topotecan Hydrochloride, and Zejula (Niraparib Tosylate Monohydrate). In some embodiments, the anti-cancer agent is gemcitabine (gem) or cisplatin.

In some embodiments, an anti-cancer agent is a pyrrolbenzodiazepine (PBD). Generally, PDBs are a class of dimerized crosslinking agents that bind to the DNA minor-groove in a sequence-specific manner, for example as described by Antonow D et al. (2011) *Chem Rev* 111: 2815–2864; Cipolla et al. (2009) *Anticancer Agents Med Chem* 9: 1–31; and Gerratana (2012) *Med Res Rev* 32: 254–293.

In some embodiments, the therapeutic agent (*e.g.*, anti-cancer agent) is an immunomodulatory moiety (*e.g.*, immunomodulatory agent). As used herein, “immunomodulatory agent” refers to a compound or molecule that increases or decreases the immune response of a subject in response to the agent. For example, an immunomodulatory agent may enhance the immune response of a subject to a tumor, *e.g.*, increase the level of inflammatory cytokines such as interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF- α). Examples of immunomodulatory agents that increase the immune response of a subject include granulocyte colony-stimulating factor (G-CSF), interferons, imiquimod, cellular membrane fractions from bacteria, certain interleukins and cytokines (*e.g.*, IL-1 β , IL-6, and TNF- α), and immune checkpoint inhibitors (*e.g.*, PD-1 inhibitors, PD1-L inhibitors, *etc.*). In some embodiments, an immunomodulatory agent may decrease the immune response of a subject (*e.g.*, mediate or achieve immunosuppression). Examples of immunosuppressive immunomodulators include but are not limited to immunosuppressive drugs (*e.g.*, glucocorticoids, cytostatics, anti-inflammatory monoclonal antibodies (*e.g.*, anti-IL-2 receptor antibodies)), and drugs targeting immunophilins (*e.g.*, ciclosporin, sirolimus, *etc.*).

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One or more therapeutic agents (*e.g.*, anti-cancer agent) may be coupled or conjugated either directly to the anti-plectin-1 antibodies of the disclosure or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. In some embodiments, multiple (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) therapeutic agents (*e.g.*,
5 anti-cancer agent molecules) are coupled or conjugated to an anti-plectin-1 antibody. For example, in some embodiments, an ADC comprises 1, 2, 3, 4, or 5 PDB molecules (*e.g.*, PDB dimers, trimers, *etc.*) conjugated to an anti-plectin-1 antibody.

In some embodiments, the antibody is coupled to the targeted agent via a linker. As used herein, the term "linker" refers to a molecule or sequence, such as an amino acid sequence, that
10 attaches, as in a bridge, one molecule or sequence to another molecule or sequence. "Linked," "conjugated," or "coupled" means attached or bound by covalent bonds, or non-covalent bonds, or other bonds, such as van der Waals forces. Antibodies described by the disclosure can be linked to the targeted agent (*e.g.*, therapeutic moiety or detectable moiety) directly, *e.g.*, as a fusion protein with protein or peptide detectable moieties (with or without an optional linking
15 sequence, *e.g.*, a flexible linker sequence) or via a chemical coupling moiety. A number of such coupling moieties are known in the art, *e.g.*, a peptide linker or a chemical linker, *e.g.*, as described in International Patent Application Publication No. WO 2009/036092. In some embodiments, the linker is a flexible amino acid sequence. Examples of flexible amino acid sequences include glycine and serine rich linkers, which comprise a stretch of two or more
20 glycine residues, (*e.g.*, GGGS; SEQ ID NO: 91). In some embodiments, the linker is a photolinker. Examples of photolinkers include ketyl-reactive benzophenone (BP), anthraquinone (AQ), nitrene-reactive nitrophenyl azide (NPA), and carbene-reactive phenyl-(trifluoromethyl)diazirine (PTD).

Pharmaceutical Compositions

25 In some aspects, the disclosure relates to pharmaceutical compositions comprising anti-plectin-1 antibodies (*e.g.*, ADCs comprising anti-plectin-1 antibodies). In some embodiments, the composition comprises an anti-plectin-1 antibody, an anti-cancer agent, and a pharmaceutically acceptable carrier. The ratio (*e.g.*, concentration ratio) of anti-plectin-1 antibody to anti-cancer agent in a composition of the disclosure can vary. In some
30 embodiments, the ratio of anti-plectin-1 antibody to anti-cancer agent ranges from about 1:100

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to about 100:1, for example any ratio therebetween. In some embodiments, the ratio (*e.g.*, concentration ratio) of anti-plectin-1 antibody to anti-cancer agent is about 1:1.

As used herein the term “pharmaceutically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions. Pharmaceutical compositions can be prepared as described below. The active ingredients may be admixed or compounded with any conventional, pharmaceutically acceptable carrier or excipient. The compositions may be sterile.

Typically, pharmaceutical compositions are formulated for delivering an effective amount of an agent (*e.g.*, a composition comprising an anti-plectin-1 antibody, or antibody drug conjugate comprising an anti-plectin-1 antibody and an anti-cancer agent). In general, an “effective amount” of an active agent refers to an amount sufficient to elicit the desired biological response (*e.g.*, killing of a cancerous cell or suppression of tumor growth). An effective amount of an agent may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated (*e.g.*, certain cancers characterized by surface expression of plectin-1), the mode of administration, and the patient.

A composition is said to be a “pharmaceutically acceptable carrier” if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers are well-known in the art. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Ed. (1990).

It will be understood by those skilled in the art that any mode of administration, vehicle or carrier conventionally employed and which is inert with respect to the active agent may be utilized for preparing and administering the pharmaceutical compositions of the present disclosure. Illustrative of such methods, vehicles and carriers are those described, for example, in Remington's Pharmaceutical Sciences, 4th ed. (1970), the disclosure of which is incorporated herein by reference. Those skilled in the art, having been exposed to the principles of the disclosure, will experience no difficulty in determining suitable and appropriate vehicles, excipients and carriers or in compounding the active ingredients therewith to form the pharmaceutical compositions of the disclosure.

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An effective amount, also referred to as a therapeutically effective amount, of a compound (for example, an anti-plectin-1 antibody or antibody drug conjugate comprising an anti-plectin-1 antibody and a targeted agent) is an amount sufficient to ameliorate at least one adverse effect associated with cancer (*e.g.*, tumor growth, metastasis). The therapeutically effective amount to be included in pharmaceutical compositions depends, in each case, upon several factors, *e.g.*, the type, size and condition of the patient to be treated, the intended mode of administration, the capacity of the patient to incorporate the intended dosage form, *etc.* Generally, an amount of active agent is included in each dosage form to provide from about 0.1 to about 250 mg/kg, and preferably from about 0.1 to about 100 mg/kg. One of ordinary skill in the art would be able to determine empirically an appropriate therapeutically effective amount.

Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and selected mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular therapeutic agent being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular nucleic acid and/or other therapeutic agent without necessitating undue experimentation.

In some cases, compounds of the disclosure are prepared in a colloidal dispersion system. Colloidal dispersion systems include lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. In some embodiments, a colloidal system of the disclosure is a liposome. Liposomes are artificial membrane vessels which are useful as a delivery vector *in vivo* or *in vitro*. It has been shown that large unilamellar vesicles (LUVs), which range in size from 0.2 - 4.0 μm can encapsulate large macromolecules.

Liposomes may be targeted to a particular tissue by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Ligands which may be useful for targeting a liposome to, for example, an smooth muscle cell include, but are not limited to: intact or fragments of molecules which interact with smooth muscle cell specific receptors and molecules, such as antibodies, which interact with the cell surface markers of cancer cells. Such ligands may easily be identified by binding assays well known to those of

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skill in the art. In still other embodiments, the liposome may be targeted to a tissue by coupling it to an antibody known in the art.

Compounds described by the disclosure may be administered alone (*e.g.*, in saline or buffer) or using any delivery vehicle known in the art. For instance the following delivery vehicles have been described: cochleates; Emulsomes; ISCOMs; liposomes; live bacterial vectors (*e.g.*, *Salmonella*, *Escherichia coli*, *Bacillus Calmette-Guérin*, *Shigella*, *Lactobacillus*); live viral vectors (*e.g.*, Vaccinia, adenovirus, Herpes simplex); microspheres; nucleic acid vaccines; polymers (*e.g.*, carboxymethylcellulose, chitosan); polymer rings; proteosomes; sodium fluoride; transgenic plants; virosomes; and, virus-like particles.

The formulations of the disclosure are administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

The term pharmaceutically-acceptable carrier means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term carrier denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present disclosure, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

In addition to the formulations described herein, the compounds may also be formulated as a depot preparation. Such long-acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium

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carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer R (1990) *Science* 249:1527-1533, which is incorporated herein by reference.

The compounds may be administered *per se* (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or

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both, and then, if necessary, shaping the product. Liquid dose units are vials or ampoules. Solid dose units are tablets, capsules and suppositories.

Treatment Methods

5 Aspects of the disclosure relate to combinations of anti-plectin-1 antibodies and anti-cancer agents, administered as a single composition or separately, that act together (*e.g.*, synergistically) to inhibit growth of certain cancer cells. Methods of measuring synergism are known and are described, for example by Chou (2010) *Cancer Res.* 70(2): 440-6. In some
10 embodiments, a combination of anti-plectin-1 antibody and one or more anti-cancer agents inhibits growth of a cell (*e.g.*, a cancer cell) by between 2-fold and 100-fold (*e.g.*, 2-fold, 4-fold, 5-fold, 10-fold, 20-fold, 25-fold, 50-fold, 75-fold, *etc.*) more than either the antibody or anti-cancer agent alone. In some embodiments, a combination of anti-plectin-1 antibody and one or more anti-cancer agents inhibits growth of a cell (*e.g.*, a cancer cell) more than 100-fold relative to either the antibody or anti-cancer agent alone.

15 Without wishing to be bound by any particular theory, compositions and ADCs described by the disclosure are useful, in some embodiments, for treating cancer characterized by surface expression of plectin-1. As used herein, "treating cancer" refers to decreasing the number of cancer cells in a patient, slowing the growth of cancer cells in a patient, reducing the metastasis of cancer cells in a patient and includes any type of response for either relieving
20 cancer symptoms or increasing the life-span of a patient.

Examples of cancers characterized by surface expression of plectin-1 include but are not limited to ovarian cancer cell, esophageal cancer cell, head and neck squamous cell carcinoma cancer cell, or pancreatic cancer cell (*e.g.*, pancreatic ductal adenocarcinoma (PDAC)). However, it should be appreciated that other cancers (such as lung cancer, bladder cancer, breast
25 cancer, esophageal cancer, mouth cancer, tongue cancer, gum cancer, skin cancer (*e.g.*, melanoma, basal cell carcinoma, Kaposi's sarcoma, *etc.*), muscle cancer, heart cancer, liver cancer, bronchial cancer, cartilage cancer, bone cancer, stomach cancer, prostate cancer, testicular cancer, cervical cancer, endometrial cancer, uterine cancer, colon cancer, colorectal, gastric cancer, kidney cancer, bladder cancer, lymphoma cancer, spleen cancer, thymus cancer,
30 thyroid cancer, brain cancer, neuronal cancer, mesothelioma, gall bladder cancer, ocular cancer (*e.g.*, cancer of the cornea, cancer of uvea, cancer of the choroids, cancer of the macula, vitreous humor cancer, *etc.*), joint cancer (such as synovium cancer), glioblastoma, white blood cell

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cancer (*e.g.*, lymphoma, leukemia, *etc.*), hereditary non-polyposis cancer (HNPC), colitis-associated cancer, *etc.*) may be characterized by surface expression of plectin-1 and/or treated using compositions and ADCs described by the disclosure. Cancers further exemplified by sarcomas (such as osteosarcoma and Kaposi's sarcoma) may, in some embodiments, be treated using compositions and ADCs described by the disclosure.

In some aspects, the disclosure provides a method for treating cancer, the method comprising administering to a subject having cancer an effective amount of a composition or ADC as described by the disclosure (*e.g.*, a composition or ADC comprising an anti-plectin-1 antibody and an anti-cancer agent). In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

Generally, antibodies and pharmaceutical compositions of the disclosure preferably contain a pharmaceutically acceptable carrier or excipient suitable for rendering the compound or mixture administrable orally as a tablet, capsule or pill, or parenterally, intravenously, intradermally, intramuscularly or subcutaneously, or transdermally.

The pharmaceutical compositions and/or ADCs can be administered by any suitable route for administering medications. A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular agent or agents selected, the particular condition being treated, and the dosage required for therapeutic efficacy. The methods of this disclosure, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces therapeutic effect without causing clinically unacceptable adverse effects. Various modes of administration are discussed herein. For use in therapy, an effective amount of the anti-plectin-1 antibody and/or other therapeutic agent can be administered to a subject by any mode that delivers the agent to the desired surface, *e.g.*, mucosal, systemic.

Administering the pharmaceutical composition of the present disclosure may be accomplished by any means known to the skilled artisan. Routes of administration include but are not limited to oral, parenteral, intravenous, intramuscular, intraperitoneal, intranasal, sublingual, intratracheal, inhalation, subcutaneous, ocular, vaginal, and rectal. Systemic routes include oral and parenteral. Several types of devices are regularly used for administration by inhalation. These types of devices include metered dose inhalers (MDI), breath-actuated MDI, dry powder inhaler (DPI), spacer/holding chambers in combination with MDI, and nebulizers.

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For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers for neutralizing internal acid conditions or may be administered without any carriers.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present disclosure may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin for use in

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an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion.

- 5 Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

- 10 Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or
15 dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

- 20 The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

- Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the compounds, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing
25 polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di-, and tri-glycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings; compressed tablets using
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conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the disclosure is contained in a form within a matrix such as those described in U.S. Pat. Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Pat. Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

The compositions and ADCs described by the disclosure can be administered to a subject (*e.g.*, a subject having cancer) on multiple occasions. In some embodiments, the number of occasions in which an antibody or composition of the disclosure is delivered to a subject is in a range of 2 to 10 times (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times). In some embodiments, an antibody or composition of the disclosure is delivered to a subject more than 10 times.

In some embodiments, a dose of a composition or ADC of the disclosure is administered to a subject no more than once per calendar day (*e.g.*, a 24-hour period). In some embodiments, a dose of a composition or ADC of the disclosure is administered to a subject no more than once per 2, 3, 4, 5, 6, or 7 calendar days. In some embodiments, a dose of a composition or ADC of the disclosure is administered to a subject no more than once per calendar week (*e.g.*, 7 calendar days). In some embodiments, a dose of composition or ADC of the disclosure is administered to a subject no more than bi-weekly (*e.g.*, once in a two calendar week period). In some embodiments, a dose of a composition or ADC of the disclosure is administered to a subject no more than once per calendar month (*e.g.*, once in 30 calendar days). In some embodiments, a dose of a composition or ADC of the disclosure is administered to a subject no more than once per six calendar months. In some embodiments, a dose of a composition or ADC of the disclosure is administered to a subject no more than once per calendar year (*e.g.*, 365 days or 366 days in a leap year).

The present disclosure is further illustrated by the following Example, which in no way should be construed as further limiting. The entire contents of all of the references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

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EXAMPLE

Cell assays

PDAC cell survival is assessed using a sulforhodamine B (SRB) protocol. Briefly, cells are seeded in 96-well plate and incubated overnight in the appropriate media. The next day, cells are treated with increasing concentrations of IgG control, anti-plec1, or Gemcitabine (gem). At day 3 post-treatment, the cells are stained with SRB and quantitated using a plate reader set at absorbance 562nm wavelength (Abs₅₆₂). An additional plate is dedicated to determine the cell number pre-treatment day 0. Percent control growth at each concentration is determined as % of control cell growth = [meanOD_{sample} - meanOD_{day0}] / [meanOD_{neg control} - meanOD_{day0}] x 100.

Percent growth inhibition is calculated as follows: %growth inhibition = 100 - [% of control cell growth].

After the IC₅₀ of anti-plec1, IgG, and gem are determined, an identical cell assay is performed to determine synergy by incubating cells with increasing drug concentrations with an equipotent anti plec1-to-gem ratio (*e.g.*, IC₅₀) that is specific to each cell line.

Determination of synergy

Synergy is calculated using the Chou-Talalay method (*e.g.*, as described in *Cancer Res.* 2010 Jan 15;70(2):440-6) to determine synergetic effect. Combination Index (CI) is then calculated for each treatment concentration tested. CI<1, CI=1, and CI>1 indicate synergism, additive effect, and antagonism, respectively. An example output is provided below, where CI: combination index; D: Dose; Fa= fraction affected; x=Fa.

$$CI = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2}$$

Fa	CI Value	Total Dose
0.9	0.10887	599.616
0.95	0.07791	1243.30
0.97	0.06153	2088.90

Effects of anti-plec1 and gemcitabine treatment

The effect of anti-plec1 treatment on cancer cell survival was examined. Clone PAb1 (also referred to as anti plec1) was observed to demonstrate the highest affinity and therapeutic effect (Figs. 1A-1B) of anti-plectin-1 antibodies tested. Treatment of cancer cells with anti-

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plec1 resulted in G0 as well as G2 growth arrest (FIG. 2A). The EC50 of anti-plec1 cells was calculated as 444.4 nM (FIG. 2B). Anti-plec1 treatment was also observed to alter cell morphology from homogenous epithelial-like shaped cells to stellar-like shaped cells by acting on microtubules and actin filaments (FIG. 2C).

- 5 Cell lines were incubated with increasing concentrations of anti-plec1 for 72 hours. Cells were analyzed via sulforhodamine B (SRB)-based cell survival assay. EC50s were calculated by logistic regression (GraphPad Prism) and reported as the concentration of monoclonal antibody (mAb) (expressed in nanomolar, nM) that reduced cell viability by 50%. Growth inhibition was limited to plectin-1-expressing cancer cells. Normal cells that have
- 10 cytoplasmic plectin-1 expression such as heart, kidney, skin, and pancreas all were unaffected by anti-plec1 treatment (Table 3; ND: not demonstrated; “/”: no data).

Table 3: Effect of anti-plec1 on cell survival after 72 hours.

Cell Line	Origin	Phenotype	Tissue Type	Plec Positivity	EC50 (nM)	
					anti-plec1	IgG
YapC	Human	Cancer	Pancreas	+++	570	ND
L3.6pl	Human	Cancer	Pancreas	++	801	ND
Panc-1	Human	Cancer	Pancreas	++	467	/
BxPC-3	Human	Cancer	Pancreas	++	363	/
MiaPACA2	Human	Cancer	Pancreas	++	140	ND
LNcaPs	Human	Cancer	Prostate	+	ND	/
HEK293T	Human	Normal	Kidney	-	ND	ND
RL14	Human	Normal	Heart	-	ND	ND
HPDE	Human	Normal	Pancreas	-	ND	ND
Keratinocyte	Human	Normal	Skin	-	ND	ND

- 15 Both cancer and normal cells were unaffected by treatment with control IgG. *In vivo* experiments with animals bearing a subcutaneous YAPC (PDAC cell line) xenograft demonstrated a dose dependent reduction in tumor volume. Animals undergoing treatment maintained body weight and were otherwise unaffected.

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Anti-plec1 therapy has been shown to be effective on cancer cell lines and *in vivo* against a treatment-resistant xenograft. As monotherapies are rarely effective in the long-term (*e.g.*, rituximab and trastuzumab), it was investigated whether anti-plec1 therapy synergizes with standard of care cancer therapies. At a 1:1 concentration ratio, anti-plec1 is synergistic in combination with Gemcitabine (gem), a standard of care therapy for pancreatic ductal adenocarcinoma (PDAC) (FIG. 3).

SEQUENCES

>SEQ ID NO: 1 – Plectin (hemidesmosomal protein 1), *Homo sapiens*; target protein underlined

10 MVAGMLMPRDQLRAIYEVLFREGVMVAKKDRRPRSLHPHVPGVTNLQVMRAMASLRARGLV
 RETFAWCHFYWYLTNEGIAHLRQYLHLPPEIVPASLQVRVRPVAMVMPPARRTPHVQAVQGPLG
 SPPKRGPLPTEEQRVYRRKELEEVSPEPVPVATTQRTLARPGPEPAPATDERDRVQKKTFTKWV
 NKHLIKAQRHISDLYEDLRDGHNLISLLEVLSGDSLPREKGRMRFHKLQNVQIALDYLRHRQVK
 LVNIRNDDIADGNPKLTLGLIWTIILHFQISDIQVSGQSEDMTAKEKLLLWSQRMVEGYQGLRCD
 15 NFTSSWRDGRLFNAIIHRHKPLLIDMNKVYRQTNLENLDQAFSVAERDLGVTRLLDPEDVDVPQ
 PDEKSIITYVSSLYDAMPVRVPDVQDGV RANELQLRWQEYRELVLLLLQWMRHHTAAFEERRFP
 SSFEEIEILWSQFLKFKEMELPAKEADKNRSKGIYQSLEGAVQAGQLKVPPGYHPLDVEKEWGK
 LHVAILEREKQLRSEFERLECLQRIVTKLQMEAGLCEEQLNQADALLQSDVRLLAAGKVPQRAG
 EVERDLDKADSMIRLLFNDVQTLKDGRHPQGEQMYRRVYRLHERLVAIRTEYNRLKAGVAAP
 20 ATQVAQVTLQSVQRRPELEDSTLRYLQDLLAWVEENQHRVDGAEWGVDLPSVEAQLGSHRGL
 HQSIEEFRAKIERARSDEGQLSPATRGAYRDCLGRLDLQYAKLLNSSKARLSLESLSFVAAAT
 KELMWLNEKEEEEVGFWDSDRNTNMTAKKESYSALMRELELKEKKIKELQNAGDRLLREDHP
 ARPTVESFQAALQTQWSWMLQLCCIEAHLKENAAYFQFFSDVREAEGQLQKLQEALRRKYSC
 DRSATVTRLEDLLQDAQDEKEQLNEYKGHL SGLAKRAKAVVQLKPRHPAHPMRGRLPLLAVC
 25 DYKQVEVTVHKGDECQLVGPAQPSHWKVLSSSGSEAAVPSVCFLVPPPNQEAQEA VTRLEAQH
 QALVTLWHQLHVD MKSLLAWQSLRRDVQLIRSWSLATFRTLKPEEQRQALHSLELHYQAFRLD
 SQDAGGFGPEDRLMAEREY GSCSHHYQQLLSLEQGAQEESRCQRCISELKDIRLQLEACETRT
 VHRLRLPLDKEPARECAQRIAEQQAQAEVEGLGKGVARLSAEAEKV LALPEPSPAAPT LRSEL
 ELTLGKLEQVRSLSAIYLEKLTISLVIRGTQGAEVLRAHEEQ LKEAQAVPATLPELEATKASLK
 30 KLRAQAEAAQPTFDALRDEL RGAQEVGERLQQRHGERDVEVERWRERVAQLLERWQAVLAQT
 DVRQRELEQLGRQLRY YRESADPLGAWLQDARRRQEIQAMPLADSQAVREQLRQE QALLEEI
 ERHGEKVEECQRFQAKQYINAIKD YELQLVTYKAQLEPVASPAKKPKVQSGSESVIQEYVDLRTH
 YSELTTLTSQYIKFISETLRMEEEEERLAEQQRAEERERLAEVEAALEKQRQLAEAHQAQAQA
 EREAKELQQRMQEEVVRREEAAVDAQQKRSIQEELQQLRQSSEAEIQA KARQAEEAERSRLRI

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EEEIRVVRLQLEATERQRGGAEGELQALRARAEEAEQKRQAQEEAERLRRQVQDESQRKRQA
EVELASRVKAEAEAAAREKQRALQALEELRLQAEAAERRLRQAEVERARQVQVALETAQRSAEA
ELQSKRASFAEKTAQLERSLQEEHVAVVAQLREEAERRAQQQAEAEERAREEAERELERWQLKAN
EALRLRLQAE EVAQQKSLAQAEAEKQKEEAEREARRRGKAE EQAVRQRELAEQELEKQRQLAE
5 GTAQQRLAAEQELIRLRAETEQQGEQQRQLLEELARLQREAAAATQKRQELEAELAKVRAEME
VLLASKARAEESRSTSEKSKQRLEAEAGRFRELAEEAARLRALAE EAKRQRQLAEEDAARQRA
EAERVLAEKLA AIGEATRLKTEAEIALKEKEAENERLRLRLAEDEAFQRRRLEEQA AQHKADIEER
LAQLRKASDSELERQKGLVEDTLRQRRQVEEEILALKASFEEKAAAGKAELELELGRIRSNAEDTL
RSKEQAELEAARQRQLAAEEERRRREAEEERVQKSLAAEEEAARQRKAAL EEVERLKAKVVEEAR
10 RLRERAEQESARQLQLAQEAAQKRLQAE EKAHAFVQQKEQELQQTLLQEEQSVLDQLRGEAE
AARRAAEEAE EARVQAEREA AQSRQVVEEAERLKQSAEEQAQARAQAQAAAEKLRKEAEQEA
ARRAQAEQAALRQKQAADAEMEKHKKFAEQTLRQKAQVEQELTTLRLQLEETDHQKNLLDEE
LQRLKAEATEAARQRSQVEEELFSVRVQMEELSKLKARIEAENRALILRDKDNTQRFLQEEAEK
MKQVAEEAARLSVAAQEAAARLRQLAEEDLAQQRALAEKMLKEKMQAVQEATRLKAEAE LLQ
15 QQKELAQEQARRLQEDKEQMAQQLA EETQGFQRTLEAERQRQLEMSAE AERLKL RVAEMSRA
QARAEEDAQRFRKQAE EIGEKLHRTELATQEKVTLVQTLEIQRQQSDHDAERLREAI AELEEREKE
KLQQEAKLLQLKSEEMQTVQQEQLLQETQALQQSFLSEKDSLQRERFIEQE KAKLEQLFQDEV
AKAQQRLREEQQRQQQQMEQERQRLVASMEEARRRQHEAE EGVRKQEELQQLEQQRRRQQEEL
LAEENQRLREQLQLLEE QHRAALAHSEEVTASQVAATKTL PNGRDALDGPAAEA EPEHSFDGLR
20 RKVSAQRLQEAGILSAEELQRLAQGHTTVDELARREDVRHYLQGRSSIAGLLL KATNEKLSVYA
ALQRQLLSPGTALILLEAQ AASGFLDPVRNRRLTVNEAVKEGVVGP ELHHKLLSAERAVTGYK
DPYTGGQISLFQAMQKGLIVREHGIRLLEAQIATGGVIDPVHSHRVPVDVAYRRGYFDEEMNRV
LADPSDDTKGFFDPNTHENLTYLQLLERCVEDPETGLCLLPLTDKAAKGGELVYTDSEARDVFE
KATVSAPFGKFQGKTVTIWEIINSEYFTA EQRRDLLRQFRTGRITVEKIIKIITVVEEQEQKGR LCF
25 EGLRSLVPAAELLESVIDRELYQQ LQRGERSVRDVAEVDTVRRALRGANVIAGVWLEEAGQK
LSIYNALKKDLLPSDMAVALLEAQAGTGHIDPAT SARLTVDEAVRAGLVGPEFHEKLLSAEKA
VTGYRDPYTGGQSVSLFQALKKGLIPREQGLRLLDAQ LSTGGIVDPSKSHRVPLDVACARGCLDE
ETSRALSAPRADAKAYSDPSTGEPATY GELQQRCRPDQLTGLSLLPLSEKAARARQEELYSELQA
RETFEKTPVEVPVGGFKGRTVTVWELISSEYFTA EQRQELLRQFRTGKVTVEKVIKILITIVEEVE
30 TLRQERLSFSGLRAPVPASELLASGVLSRAQFEQLKD GKTTVKDLSELG SVRTLQGGSGCLAGIY
LEDTKEKVS IYEAMRRGLLRATTAALLLEAQ AATGFLVDPVRNQRLYVHEAVKAGVVGP ELHE
QLLSAEKAVTGYRDPYSGSTISLFQAMQKGLVLRQH GIRLLEAQIATGGIIDPVHSHRVPVDVAY
QRGYFSEEMNRVLADPSDDTKGFFDPNTHENLTYRQLLERCVEDPETGLRLLPLKGAEKAEVVE
TTQVYTEETTRAFEETQIDIPGGGSHGGSTMSLWEVMQSDLIPEEQRAQLMADFQAGRVTKER
35 MIIIIIEIEKTEIIRQQGLASYDYVRRRLTAEDLFEARIISLETYNLLREGTRSLREALEAESAWCYL

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YGTGSVAGVYLPGRQTLSTYQALKKGLLSAEVARLLLEAQAATGFLLDPVKGERLTVDEAVRK
 GLVGPELHDLRLSAERA VTYRDPYTEQTISLFQAMKKELIPTEEALRLLEAQLATGGIVDPRLG
 FHLPLEVAYQRGYLNKDTHTDQLSEPSEVRSYVDPSTDERLSYTQLLRRCRRDDGTGQLLLPLSD
 ARKLTFRGLRKQITMEELVRSQVMDEATALQLREGLTSIEEVTKNLQKFLEGTSCIAGVFVDATK
 5 ERLSVYQAMKKGIIRPGTAFELLEAQAATGYVIDPIKGLKLTVEEAVRMGIVGPEFKDKLLSAER
 AVTGYKDPYSGKLISLFQAMKKGLILKDHGIRLLEAQIATGGIIDPEESHRLPVEVAYKRGLFDEE
 MNEILTDPSDDTKGFFDPNTEENLTYLQLMERCITDPQTGLCLLPLKEKKRERKTSSKSSVRKRR
 VVIVDPETGKEMSVYEA YRKGLIDHQTYLELSECEWEETISSSDGVVKSMIIDRRSGRQYDID
DAIAKNLIDRSALDQYRAGTLSITEFADMLSGNAGGFRSRSSSVGSSSSYPISPAVSRTQLASWSD
 10 PTEETGPVAGILDTETLEKVSITEAMHRNLVDNITGQRLLEAQACTGGIIDPSTGERFPVTDVANK
GLVDKIMVDRINLAQKAFCGFEDPRTKTKMSAAQALKKGWLYYEAGQRFLEVQYLTGGLIEPD
TPGRVPLDEALQRGTVDARTAQKLRDVGAYSKYLTCPKTKLKISYKDALDRSMVEEGTGLRLL
EAAAQSTKGYYSPYSVSGSGSTAGSRTGSRTGSRAGSRRGSFDATGSGFSMTFSSSSYSSSGYGR
RYASGSSASLGGPESAVA

15 >SEQ ID NO: 2 – Plectin (hemidesmosomal protein 1), *Homo sapiens*; target protein underlined
 SSSDGVVKSMIIDRRSGRQYDIDDAIAKNLIDRSALDQYRAGTLSITEFADMLSGNAGGFRSRSS
 VGSSSSYPISPAVSRTQLASWSDPTEETGPVAGILDTETLEKVSITEAMHRNLVDNITGQRLLEAQ
 ACTGGIIDPSTGERFPVTDVANKGLVDKIMVDRINLAQKAFCGFEDPRTKTKMSAAQALKKGW
 20 LYYEAGQRFLEVQYLTGGLIEPDTPGRVPLDEALQRTVDARTAQKLRDVGAYS KYLTCPKTK
 LKISYKDALDRSMVEEGTGLRLL EAAAQSTKGY YSPYSVSGSGSTAGSRTGSRTGS RAGSR
 RG SFDATGSGFSMTFSSSSYSSSGYGR RYASGSSASLGGPESAVA

Pab2 Sequences

Name	Sequence	SEQ ID NO:
Pab2 Heavy Chain	ATGAACTTCGGGCTCAGCTTGATTTTCCTTGCCCTCATTTTA AAAGGTGTCCAGTGTGAGGTGCAGCTGGTGGAGTCTGGGG GAGACTTGGTGAAGCCTGGAGGGTCCCTGAACTCTCCTGT GCAGCCTCTGGATTCACTTTCAGTAGGTATGGCATGTCTTG GGTTCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTCGCA ACCATTAGTATTGGTGGTACTTACACCTACTATCCAGACAG TATGAAGGGGCGATTACCATCTCCAGAGACAATGCCAAG AACACCCTGTACCTGCAAATGAGCAGTCTGAAGTCTGAGG ACACAGCCATGTATTACTGTGCAAGACGGGGGTATGGTAA CTACTCTTACTATGGTATGGACTACTGGGGTCAAGGAACCT CAGTCACCGTCTCCTCAGCCAAAACGACACCCCCATCTGTC TATCCACTGGCCCCTGGATCTGCTGCCCAAATAACTCCAT GGTGACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGC	3

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	CAGTGACAGTGACCTGGAACCTCTGGATCCCTGTCCAGCGGT GTGCACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACAC TCTGAGCAGCTCAGTGACTGTCCCCTCCAGCACCTGGCCCA GCGAGACCGTCACCTGCAACGTTGCCACCCGGCCAGCAG CACCAAGGTGGACAAGAAAATTGTGCCCAGGGATTGTGGT TGTAAGCCTTGCATATGTACAGTCCCAGAAGTATCATCTGT CTTCATCTTCCCCCAAGCCCAAGGATGTGCTCACCATTA CTCTGACTCCTAAGGTCACGTGTGTTGTGGTAGACATCAGC AAGGATGATCCCGAGGTCCAGTTCAGCTGGTTTGTAGATGA TGTGGAGGTGCACACAGCTCAGACGCAACCCCGGGAGGAG CAGTTCAACAGCACTTTCGCTCAGTCAGTGAACCTCCCAT CATGCACCAGGACTGGCTCAATGGCAAGGAGTTCAAATGC AGGGTCAACAGTGCAGCTTTCCTGCCCCCATCGAGAAAA CCATCTCCAAAACCAAGGCAGACCGAAGGCTCCACAGGT GTACACCATTCCACCTCCCAAGGAGCAGATGGCCAAGGAT AAAGTCAGTCTGACCTGCATGATAACAGACTTCTTCCCTGA AGACATTACTGTGGAGTGGCAGTGGGAATGGGCAGCCAGCG GAGAACTACAAGAACACTCAGCCCATCATGGACACAGATG GCTCTTACTTCGTCTACAGCAAGCTCAATGTGCAGAAGAGC AACTGGGAGGCAGGAAATACTTTCACCTGCTCTGTGTTACA TGAGGGCCTGCACAACCACCATACTGAGAAGAGCCTCTCC CACTCTCCTGGTAAATGA	
Pab2 Heavy Chain Leader	ATGAACTTCGGGCTCAGCTTGATTTTCCTTGCCCTCATTTTA AAAGGTGTCCAGTGT	4
Pab2 Heavy Chain FR1	GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTGAAGC CTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTCTGGATTC ACTTTCAGT	5
Pab2 Heavy Chain CDR1	AGGTATGGCATGTCT	6
Pab2 Heavy Chain FR2	TGGGTTCCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTCG CA	7
Pab2 Heavy Chain CDR2	ACCATTAGTATTGGTGGTACTTACACCTACTATCCAGACAG TATGAAGGGG	8
Pab2 Heavy Chain FR 3	CGATTCAACCATCTCCAGAGACAATGCCAAGAACACCCTGT ACCTGCAAATGAGCAGTCTGAAGTCTGAGGACACAGCCAT GTATTACTGTGCAAGA	9
Pab2 Heavy Chain CDR3	CGGGGGTATGGTAACTACTCTTACTATGGTATGGACTAC	10
Pab2 Heavy Chain FR 4	TGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA	11
Pab2 Heavy Chain Variable Region	GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTGAAGC CTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTCTGGATTC ACTTTCAGTAGGTATGGCATGTCTTGGGTTCCGCCAGACTCC AGACAAGAGGCTGGAGTGGGTCCGAACCATTAGTATTGGT GGTACTTACACCTACTATCCAGACAGTATGAAGGGGGCGATT CACCATCTCCAGAGACAATGCCAAGAACACCCTGTACCTG CAAATGAGCAGTCTGAAGTCTGAGGACACAGCCATGTATT ACTGTGCAAGACGGGGGTATGGTAACTACTCTTACTATGGT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTC A	12

Pab2 Heavy Chain Constant Region	GCCAAAACGACACCCCATCTGTCTATCCACTGGCCCCTGG ATCTGCTGCCCAAACCTAACTCCATGGTGACCCTGGGATGCC TGGTCAAGGGCTATTTCCCTGAGCCAGTGACAGTGACCTGG AACTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCCAGC TGTCTGCAGTCTGACCTCTACACTCTGAGCAGCTCAGTGA CTGTCCCCTCCAGCACCTGGCCCAGCGAGACCGTCACCTGC AACGTTGCCCACCCGGCCAGCAGCACCAAGGTGGACAAGA AAATTGTGCCCAGGGATTGTGGTTGTAAGCCTTGCATATGT ACAGTCCCAGAAGTATCATCTGTCTTCATCTTCCCCCAA GCCCAAGGATGTGCTCACCATTACTCTGACTCCTAAGGTCA CGTGTGTTGTGGTAGACATCAGCAAGGATGATCCCGAGGT CCAGTTCAGCTGGTTTGTAGATGATGTGGAGGTGCACACAG CTCAGACGCAACCCCGGGAGGAGCAGTTCAACAGCACTTT CCGCTCAGTCAGTGAACCTTCCCATCATGCACCAGGACTGGC TCAATGGCAAGGAGTTCAAATGCAGGGTCAACAGTGCAGC TTTCCTGCCCCCATCGAGAAAACCATCTCCAAAACCAAAG GCAGACCGAAGGCTCCACAGGTGTACACCATTCCACCTCCC AAGGAGCAGATGGCCAAGGATAAAGTCAGTCTGACCTGCA TGATAACAGACTTCTTCCCTGAAGACATTACTGTGGAGTGG CAGTGGAATGGGCAGCCAGCGGAGAACTACAAGAACA AGCCCATCATGGACACAGATGGCTCTTACTTCGTCTACAGC AAGCTCAATGTGCAGAAGAGCAACTGGGAGGCAGGAAATA CTTTCACCTGCTCTGTGTTACATGAGGGCCTGCACAACCAC CATACTGAGAAGAGCCTCTCCCACTCTCCTGGTAAA	13
Pab2 Heavy Chain	MNFGLSLIFLALILKGVQCEVQLVESGGDLVKPGGSLKLSCAA SGFTFSRYGMSWVRQTPDKRLEWVATISIGGTYTYYPDSMKG RFTISRDNKNTLYLQMSSLKSEDTAMYYCARRGYGNYSYY GMDYWGQGTSVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLG CLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSD	14
Pab2 Heavy Chain Leader	MNFGLSLIFLALILKGVQC	15
Pab2 Heavy Chain FR1	EVQLVESGGDLVKPGGSLKLSCAASGFTFS	16
Pab2 Heavy Chain CDR1	RYGMS	17
Pab2 Heavy Chain FR2	WVRQTPDKRLEWVA	18
Pab2 Heavy Chain CDR2	TISIGGTYTYYPDSMKG	19
Pab2 Heavy Chain FR 3	RFTISRDNKNTLYLQMSSLKSEDTAMYYCAR	20
Pab2 Heavy Chain CDR3	RGYGNYSYYGMDY	21
Pab2 Heavy Chain FR 4	WGQGTSVTVSS	22
Pab2 Heavy Chain Variable Region	EVQLVESGGDLVKPGGSLKLSCAASGFTFSRYGMSWVRQTPD KRLEWVATISIGGTYTYYPDSMKGRFTISRDNKNTLYLQMS SLKSEDTAMYYCARRGYGNYSYYGMDYWGQGTSVTVSS	23
Pab2 Heavy Chain Constant Region	AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWN SGSLSSGVHTFPAVLQSDLYTLSSSVTPSPSTWPSETVTCNVA	24

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	HPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTI TLTPKVTCTVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQ FNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISK KGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQ WNGQPAENYKNTQPIMDTDGSYFVYSKLVQKSNWEAGNTF TCSVLHEGLHNHHTTEKSLSHSPGK	
Pab2 Light Chain	ATGAGGTTCTCTGCTCAGCTTCTGGGGCTGCTTGTGCTCTG GATCCCTGGATCCACTGCAGATATTGTGATGACGCAGGCTG CATTCTCCAATCCAGTCACTCTTGGAACATCAGCTTCCATC TCCTGCAGGTCTAGTAAGAGTCTCCTACATAGTAATGGCAT CACTTATTTGTATTGGTATCTGCAGAAGCCAGGCCAGTCTC CTCAGTCTCCTGATTTATCAGATGTCCAACCTTGCCTCAGGA GTCCCAGACAGGTTTCAGTAGCAGTGGGTCAGGAACTGATT TCACACTGAGAATCAGCAGAGTGGAGGCTGAGGATGTGGG TGTTTATTACTGTGCTCAAAATCTAGAACTTCCGCTCACGTT CGGTGCTGGGACCAAGCTGGAGCTGAAACGGGCTGATGCT GCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTT AACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACT TCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGG CAGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGAT CAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCC TCACGTTGACCAAGGACGAGTATGAACGACATAACAGCTA TACCTGTGAGGCCACTACAAGACATCAACTTCACCCATTG TCAAGAGCTTCAACAGGAATGAGTGTTAG	25
Pab2 Light Chain Leader	ATGAGGTTCTCTGCTCAGCTTCTGGGGCTGCTTGTGCTCTG GATCCCTGGATCCACTGCA	26
Pab2 Light Chain FR1	GATATTGTGATGACGCAGGCTGCATTCTCCAATCCAGTCAC TCTTGGAACATCAGCTTCCATCTCCTGC	27
Pab2 Light Chain CDR1	AGGTCTAGTAAGAGTCTCCTACATAGTAATGGCATCACTTA TTGTAT	28
Pab2 Light Chain FR2	TGGTATCTGCAGAAGCCAGGCCAGTCTCCTCAGCTCCTGAT TTAT	29
Pab2 Light Chain CDR2	CAGATGTCCAACCTTGCCTCA	30
Pab2 Light Chain FR 3	GGAGTCCCAGACAGGTTTCAGTAGCAGTGGGTCAGGAACTG ATTTCACTGAGAATCAGCAGAGTGGAGGCTGAGGATGT GGGTGTTTATTACTGT	31
Pab2 Light Chain CDR3	GCTCAAAATCTAGAACTTCCGCTCACG	32
Pab2 Light Chain FR 4	TTCGGTGCTGGGACCAAGCTGGAGCTGAAA	33
Pab2 Light Chain Variable Region	GATATTGTGATGACGCAGGCTGCATTCTCCAATCCAGTCAC TCTTGGAACATCAGCTTCCATCTCCTGCAGGTC TAGTAAGAGTCTCCTACATAGTAATGGCATCACTTATTTGT ATTGGTATCTGCAGAAGCCAGGCCAGTCTCCTCAGTCTCTG ATTTATCAGATGTCCAACCTTGCCTCAGGAGTCCCAGACAG GTTTCAGTAGCAGTGGGTCAGGAACTGATTTCACTGAGA ATCAGCAGAGTGGAGGCTGAGGATGTGGGTGTTTATTACT GTGCTCAAAATCTAGAACTTCCGCTCACGTTCCGGTGCTGGG ACCAAGCTGGAGCTGAAA	34

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Pab2 Light Chain Constant Region	CTGTGCTCAAAATCTAGAACTTCCGCTCACGTTCCGGTGCTG GGACCAAGCTGGAGCTGAAACGGGCTGATGCTGCACCAAC TGTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTG GAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCC AAAGACATCAATGTCAAGTGAAGATTGATGGCAGTGAAC GACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAG CAAAGACAGCACCTACAGCATGAGCAGCACCCCTCACGTTG ACCAAGGACGAGTATGAACGACATAACAGCTATACCTGTG AGGCCACTCACA AGACATCAACTTCACCCATTGTCAAGAGCTTCAACAGGAAT GAGTGT	35
Pab2 Light Chain	MRFSAQLLGLLVLPWGSTADIVMTQAAFSNPVTLGTSASISC RSSKSLHLSNGITYLYWYLQKPGQSPQLLIYQMSNLAGVDPDR FSSSGSGTDFTLRISRVEAEDVGVYYCAQNLELPLTFGAGTKL ELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVK WKIDGSRQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYER HNSYTCEATHKTSTSPIVKSFNRENC	36
Pab2 Light Chain Leader	MRFSAQLLGLLVLPWGSTA	37
Pab2 Light Chain FR1	DIVMTQAAFSNPVTLGTSASISC	38
Pab2 Light Chain CDR1	RSSKSLHLSNGITYLY	39
Pab2 Light Chain FR2	WYLQKPGQSPQLLIY	40
Pab2 Light Chain CDR2	QMSNLAG	41
Pab2 Light Chain FR 3	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	42
Pab2 Light Chain CDR3	AQNLELPLT	43
Pab2 Light Chain FR 4	FGAGTKLELK	44
Pab2 Light Chain Variable Region	DIVMTQAAFSNPVTLGTSASISCRSSKSLHLSNGITYLYWYLQ KPGQSPQLLIYQMSNLAGVDPDRFSSSGSGTDFTLRISRVEAED VGVYYCAQNLELPLTFGAGTKLELK	45
Pab2 Light Chain Constant Region	RADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI DGSRQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYERHNS YTCEATHKTSTSPIVKSFNRENC	46

Pab1 Sequences

Name	Sequence	SEQ ID NO:
Pab1 Heavy Chain	ATGGCTTGGGTGTGGACCTTGCTATTCCTGATGGCAGCTGC CCAAAGTATCCAAGCACAGATCCAGTTGGTGCAGTCTGGA CCTGAGCTGAAGAAGCCTGGAGAGACAGTCAAGATCTCCT GCAAGGCTTCTGGTTATACCTTCACAGACTATTCAATGCAC TGGGTGAAGCAGGCTCCAGGAAAGGGTTTAAAGTGGATGG	47

- 32 -

	GCTGGATAAACTGAGACTGGTGAGCCAACATATGCAGATGACTTCAAGGGACGGTTTGCCTTCTCTTTGGAAACCTCTGCCAGCACTGCCTATTTGCAGATCAACAACCTCAAAAATGAGGACACGGCTAC ATATTTCTGTGCCCCCGGAGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCAGCCAAAACAACACCCCCATCAGTCTATCCACTGGCCCCCTGGGTGTGGAGATACAACCTGGTTCTCCGTGACTCTGGGATGCCTGGTCAAGGGCTACTTCCCTGAGTCAGTGACTGTGACTTGGAACCTCTGGATCCCTGTCCAGCAGTGTGCACACCTTCCCAGCTCTCCTGCAGTCTGGACTCTACACTATGAGCAGCTCAGTGACTGTCCCCTCCAGCACCTGGCCAAGTCAGACCGTCACCTGCAGCGTTGCTCACCCAGCCAGCAGCACCAACGGTGGACAAAAAACTTGAGCCCAGCGGGCCATTTCAACAATCAACCCCTGTCCTCCATGCAAGGAGTGTCACAAATGCCCAGCTCCTAACCTCGAGGGTGGACCATCCGTTTCATCTTCCCTCCAAATATCAAGGATGTACTCATGATCTCCCTGACACCCAAGGTCACGTGTGTGGTGGTGGATGTGAGCGAGGATGACCCAGACGTCCAGATCAGCTGGTTTGTGAACAACGTGGAAGTACACACAGCTCAGACACAAACCCATAGAGAGGATTACAACAGTACTATCCGGGTGGTCAGCACCCCTCCCCATCCAGCACCAAGTGGATGAGTGGCAAGGAGTTCAAATGCAAGGTCAACAACAAGACCTCCCATCACCCATCGAGAGAACCATCTCAAAAATTAAAGGGCTAGTCAGAGCTCCACAAGTATACATCTTGCCGCCACCAGCAGAGCAGTTGTCCAGGAAGATGTCAGTCTCACTTGCCTGGTTCGTGGGCTTCAACCCTGGAGACATCAGTGTGGAGTGGACCAGCAATGGGCATACAGAGGAGAACTACAAGGACACCGCACCAAGTCTGGACTCTGACGGTTCTTACTTCATATATAGCAAGCTCAATATGAAAACAA GCAAGTGGGAGAAAACAGATTCTTCTCATGCAACGTGAGACACGAGGGTCTGAAAAATTACTACCTGAAGAAGACCATCTCCCGGTCTCCGGGTAAATGA	
Pab1 Heavy Chain Leader	ATGGCTTGGGTGTGGACCTTGCTATTCTGATGGCAGCTGCCAAAGTATCCAAGCA	48
Pab1 Heavy Chain FR1	CAGATCCAGTTGGTGCAGTCTGGACCTGAGCTGAAGAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGGCTTCTGGTTATACCTTCACA	49
Pab1 Heavy Chain CDR1	GACTATTCAATGCAC	50
Pab1 Heavy Chain FR2	TGGGTGAAGCAGGCTCCAGGAAAGGGTTTAAAGTGGATGGGC	51
Pab1 Heavy Chain CDR2	TGGATAAACTGAGACTGGTGAGCCAACATATGCAGATGACTTCAAGGGA	52
Pab1 Heavy Chain FR 3	CGGTTTGCCTTCTCTTTGGAAACCTCTGCCAGCACTGCCTATTGTCAGATCAACAACCTCAAAAATGAGGACACGGCTACATATTCTGTGCCCCC	53
Pab1 Heavy Chain CDR3	GGAGGGTTTGCTTAC	54
Pab1 Heavy Chain FR 4	TGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA	55
Pab1 Heavy Chain	CAGATCCAGTTGGTGCAGTCTGGACCTGAGCTGAAGAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGGCTTCTGGTTAT	56

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Variable Region	ACCTTCACAGACTATTCAATGCACTGGGTGAAGCAGGCTCC AGGAAAGGGTTTAAAGTGGATGGGCTGGATAAACTGAG ACTGGTGAGCCAACATATGCAGATGACTTCAAGGGACGGT TTGCCTTCTCTTTGGAAACCTCTGCCAGCACTGCCTATTTGC AGATCAACAACCTCAAAAATGAGGACACGGCTACATATTT CTGTGCCCCCGGAGGGTTTGCTTACTGGGGCCAAGGGACTC TGGTCACTGTCTCTGCA	
Pab1 Heavy Chain Constant Region	GCCAAAACAACACCCCCATCAGTCTATCCACTGGCCCCTGG GTGTGGAGATACAACTGGTTCCTCCGTGACTCTGGGATGCC TGGTCAAGGGCTACTTCCCTGAGTCAGTGACTGTGACTTGG AACTCTGGATCCCTGTCCAGCAGTGTGCACACCTTCCCAGC TCTCCTGCAGTCTGGACTCTACACTATGAGCAGCTCAGTGA CTGTCCCCTCCAGCACCTGGCCAAGTCAGACCGTCACCTGC AGCGTTGCTCACCCAGCCAGCAGCACCCACGGTGGACAAAA AACTTGAGCCCAGCGGGCCCATTTCAACAATCAACCCCTGT CCTCCATGCAAGGAGTGTCACAAATGCCAGCTCCTAACCT CGAGGGTGGACCATCCGTCTTCATCTTCCCTCCAAATATCA AGGATGTACTCATGATCTCCCTGACACCCAAGGTCACGTGT GTGGTGGTGGATGTGAGCGAGGATGACCCAGACGTCCAGA TCAGCTGGTTTTGTGAACAACGTGGAAGTACACACAGCTCA GACACAAACCCATAGAGAGGATTACAACAGTACTATCCGG GTGGTCAGCACCCCTCCCCATCCAGCACCCAGGACTGGATGA GTGGCAAGGAGTTCAAATGCAAGGTCAACAACAAAGACCT CCCATCACCCATCGAGAGAACCATCTCAAAAATTAAGGG CTAGTCAGAGCTCCACAAGTATACATCTTGCCGCCACCAGC AGAGCAGTT GTCCAGGAAAGATGTCAGTCTCACTTGCCTGGTCTGGGGCT TCAACCCCTGGAGACATCAGTGTGGAGTGGACCAGCAATGG GCATACAGAGGAGAACTACAAGGACACCGCACCCAGTCTTG GACTCTGACGGTTCTTACTTCATATATAGCAAGCTCAATAT GAAAACAAGCAAGTGGGAGAAAACAGATTCCTTCTCATGC AACGTGAGACACGAGGGTCTGAAAAATTACTACCTGAAGA AGACCATCTCCCGGTCTCCGGGTAAA	57
Pab1 Heavy Chain	MAWVWTLFLMAAAQSIQAQIQLVQSGPELKKPGETVKISCK ASGYTFTDYSMHVWKQAPGKGLKWMGWINTETGEPTYADD FKGRFAFSLETSASTAYLQINNLIKNETATYFCAPGGFAYWG QGTLVTVSAAKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYF PESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWP SQTVTCSVAHPASSTTVDDKKLEPSGPSTINPCPPCKECHKCPA PNLEGGPSVFIFPPNIKDVLMLSLTPKVTCTVVDVSEDDPDVQI SWFVNNVEVHTAQQTTHREDYNSTIRVVSTLPIQHQDWMSG KEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSR KDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSGD SYFIYSKLNMKTSKWEKTDSEFCNVRHEGLKNYYLKKTISRSP GK	58
Pab1 Heavy Chain Leader	MAWVWTLFLMAAAQSIQA	59
Pab1 Heavy Chain FR1	QIQLVQSGPELKKPGETVKISCKASGYTFT	60
Pab1 Heavy Chain CDR1	DYSMH	61

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Pab1 Heavy Chain FR2	WVKQAPGKGLKWMG	62
Pab1 Heavy Chain CDR2	WINTETGEPTYADDFKG	63
Pab1 Heavy Chain FR 3	RFAFSLETSASTAYLQINNLNKEDTATYFCAP	64
PAb1 Heavy Chain CDR3	GGFAY	65
PAb1 Heavy Chain FR 4	WGQGLTVTVSA	66
PAb1 Heavy Chain Variable Region	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSMHWVKQAPG KGLKWMGWINTETGEPTYADDFKGRFAFSLETSASTAYLQIN NLKEDTATYFCAPGGFAYWGQGLTVTVSA	67
PAb1 Heavy Chain Constant Region	AKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESVTVTN SGLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCVA HPASSTTVDKKLEPSGPSTINPCPPCKECHKCPAPNLEGGPSV FIFPPNIKDVLMISLTPKVTCTVVDVSEDDPDVQISWVNNVE VHTAQQTTHREDYNSTIRVVSTLPIQHQDWMSGKEFKCKVN NKDLPSPERTISKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLV VGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFIYSKLN MKTSKWEKTDSEFCNVRHEGLKNYYLKKTISRSPGK	68
PAb1 Light Chain	ATGAGGTGCCTAGCTGAGTTCCTGGGGCTGCTTGCTCTG GATCCCTGGAGCCATTGGGGATATTGTGATGACTCAGGCTG CACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCATC TCCTGCAGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAA CACTTACTTGTATTGGTTCCTGCAGAGGCCAGGCCAGTCTC CTCAGTCTCTGATATATCGGATGTCCAACCTTGCCTCAGGA GTCCCAGACAGGTTTCAGTGGCAGTGGGTCAGGAACTGCTTT CACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGTGGGT GTTTATTACTGTATGCAACATCTAGAATATCCGCTCACGTT CGGTGCTGGGACCAAGCTGGAGCTGAAACGGGCTGATGCT GCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTT AACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACT TCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGG CAGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGAT CAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCC TCACGTTGACCAAGGACGAGTATGAACGACATAACAGCTA TACCTGTGAGGCCACTCACAAGACATCAACTTCACCCATTG TCAAGAGCTTCAACAGGAATGAGTGTTAG	69
PAb1 Light Chain Leader	ATGAGGTGCCTAGCTGAGTTCCTGGGGCTGCTTGCTCTG GATCCCTGGAGCCATTGGG	70
PAb1 Light Chain FR1	GATATTGTGATGACTCAGGCTGCACCCTCTGTACCTGTAC TCCTGGAGAGTCAGTATCCATCTCCTGC	71
PAb1 Light Chain CDR1	AGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACACTTA CTTGTAT	72
PAb1 Light Chain FR2	TGGTTCCTGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGAT ATAT	73
PAb1 Light Chain CDR2	CGGATGTCCAACCTTGCCTCA	74
PAb1 Light Chain	GGAGTCCCAGACAGGTTTCAGTGGCAGTGGGTCAGGAACTG	75

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FR 3	CTTTCACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGT GGGTGTTTATTACTGT	
PAb1 Light Chain CDR3	ATGCAACATCTAGAATATCCGCTCACG	76
PAb1 Light Chain FR 4	TTCGGTGCTGGGACCAAGCTGGAGCTGAAA	77
PAb1 Light Chain Variable Region	GATATTGTGATGACTCAGGCTGCACCCTCTGTACCTGTCAC TCCTGGAGAGTCAGTATCCATCTCCTGCAGGTCTAGTAAGA GTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTC CTGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGATATATCG GATGTCCAACCTTGCTCAGGAGTCCCAGACAGGTTTCAGTG GCAGTGGGTCAGGAAGTCTTTCACACTGAGAATCAGTAG AGTGGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAAC ATCTAGAATATCCGCTCACGTTTCGGTGCTGGGACCAAGCTG GAGCTGAAA	78
PAb1 Light Chain Constant Region	CGGGCTGATGCTGCACCAACTGTATCCATCTTCCCACCATC CAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCT TCTTGAACAACTTCTACCCCAAAGACATCAATGTCAAGTGG AAGATTGATGGCAGTGAACGACAAAATGGCGTCCTGAACA GTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGCAT GAGCAGCACCCCTCACGTTGACCAAGGACGAGTATGAACGA CATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAA CTTCACCCATTGTCAAGAGCTTCAACAGGAATGAGTGT	79
PAb1 Light Chain	MRCLAEFLGLLVLWIPGAIGDIVMTQAAPSVVPTPGESVSISC RSSKSLHLSNGNTYLYWFLQRPQGSPQLLIYRMSNLASGVPD RFSGSGSGTAFTLRISRVEAEDVGVIYCMQHLEYPLTFGAGT KLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV KWKIDGSRQNGVLNSWTDQDSKDYMSSTLTTLTKDEYE RHNSYTCEATHKTSTSPIVKSFNRENEC	80
PAb1 Light Chain Leader	MRCLAEFLGLLVLWIPGAIG	81
PAb1 Light Chain FR1	DIVMTQAAPSVVPTPGESVSISC	82
PAb1 Light Chain CDR1	RSSKSLHLSNGNTYLY	83
PAb1 Light Chain FR2	WFLQRPQGSPQLLIY	84
PAb1 Light Chain CDR2	RMSNLAS	85
PAb1 Light Chain FR 3	GVPDRFSGSGSGTAFTLRISRVEAEDVGVIYCMQHLEYPLT	86
PAb1 Light Chain CDR3	MQHLEYPLT	87
PAb1 Light Chain FR 4	FGAGTKLELKR	88
PAb1 Light Chain Variable Region	DIVMTQAAPSVVPTPGESVSISCRSSKSLHLSNGNTYLYWFLQ RPGQSPQLLIYRMSNLASGVPDRFSGSGSGTAFTLRISRVEAED VGVIYCMQHLEYPLTFGAGTKLELKR	89
PAb1 Light Chain	ADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKID GSRQNGVLNSWTDQDSKDYMSSTLTTLTKDEYERHNSYT	90

Constant Region	CEATHKTSTSPIVKSFNRECE	
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CLAIMS

What is claimed is:

1. A composition comprising:

- (i) an antibody that specifically binds to plectin-1 exposed on the surface of a cancer cell; and
- (ii) an anti-cancer agent,

wherein the antibody and the anticancer agent are not linked.

2. A composition comprising:

- (i) an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2; and
- (ii) an anti-cancer agent,

wherein the antibody and the anti-cancer agent are not linked.

3. The composition of claim 2, wherein the antibody or antigen binding fragment comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 23 or SEQ ID NO: 67.

4. The composition of claim 3, wherein the antibody or antigen binding fragment further comprises a light chain variable region having a sequence set forth as: SEQ ID NO: 45 or SEQ ID NO: 89.

5. The composition of any one of claims 1 to 4, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 23 and a light chain variable region having a sequence set forth as: SEQ ID NO: 45.

6. The composition of any one of claims 1 to 4, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 67 and a light chain variable region having a sequence set forth as: SEQ ID NO: 89.

7. The composition of any one of claims 2 to 6, wherein the antibody or antigen binding fragment binds to cell-surface exposed plectin-1.

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8. The composition of any one of claims 1 to 7, wherein the anti-cancer agent is selected from the group consisting of Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Adrucil (Fluorouracil), Afinitor (Everolimus), Efudex (Fluorouracil), Erlotinib Hydrochloride, Everolimus, Fluoroplex (Fluorouracil), Fluorouracil, Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Mitomycin C, Mitozytrex (Mitomycin C), Mutamycin (Mitomycin C), Paclitaxel Albumin-stabilized Nanoparticle Formulation, Sunitinib Malate, Sutent (Sunitinib Malate), and Tarceva (Erlotinib Hydrochloride), Altretamine, Alkeran (Melphalan), Avastin (Bevacizumab), Bevacizumab, Carboplatin, Clade (Cyclophosphamide), Cisplatin, Cyclophosphamide, Cytosan (Cyclophosphamide), Doxorubicin Hydrochloride, Dox-SL (Doxorubicin Hydrochloride Liposome), DOXIL (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Evacet (Doxorubicin Hydrochloride Liposome), Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Hycamtin (Topotecan Hydrochloride), LipoDox (Doxorubicin Hydrochloride Liposome), Lynparza (Olaparib), Melphalan, Neosar (Cyclophosphamide), Niraparib Tosylate Monohydrate, Olaparib, Paclitaxel, Paraplat (Carboplatin), Paraplatin (Carboplatin), Platinol (Cisplatin), Platinol-AQ (Cisplatin), Rubraca (Rucaparib Camsylate), Rucaparib Camsylate, Taxol (Paclitaxel), Thiotepa, Topotecan Hydrochloride, Zejula (Niraparib Tosylate Monohydrate).

9. The composition of any one of claims 1 to 8, wherein the anti-cancer agent is Gemcitabine or Cisplatin.

10. The composition of any one of claims 1 to 9, wherein the anti-plectin-1 antibody and the anti-cancer agent act synergistically (*e.g.*, as measured by the Chou-Talalay method).

11. An antibody-drug-conjugate (ADC) comprising an antibody or antigen binding fragment that specifically binds to plectin-1 exposed on the surface of a cancer cell linked to one or more anti-cancer agent molecules.

12. An antibody-drug-conjugate (ADC) comprising an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2 linked to one or more anti-cancer agent molecules.

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13. The ADC of claim 11 or 12, wherein the one or more anti-cancer agent molecules are directly linked to the antibody or antigen binding fragment.

5 14. The ADC of claim 11 or 12, wherein the one or more anti-cancer agent molecules are indirectly linked to the antibody or antigen binding fragment via a linker, optionally a photolinker or a flexible amino acid sequence linker.

10 15. The ADC of any one of claims 11 to 14, wherein 2, 3, 4, or 5 anti-cancer agent molecules are linked to the antibody or antigen binding fragment.

16. The ADC of any one of claims 11 to 15, wherein each of the one or more anti-cancer agent molecules is auristatin or pyrrolobenzodiazepine (PBD), optionally wherein each PBD is a PBD dimer.

15 17. The ADC of any one of claims 11 to 16, wherein the antibody or antigen binding fragment comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 23 or SEQ ID NO: 67.

20 18. The ADC of any one of claims 11 to 16, wherein the antibody or antigen binding fragment further comprises a light chain variable region having a sequence set forth as: SEQ ID NO: 45 or SEQ ID NO: 89.

25 19. The ADC of any one of claims 11 to 18, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 23 and a light chain variable region having a sequence set forth as: SEQ ID NO: 45.

30 20. The ADC of any one of claims 11 to 18, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 67 and a light chain variable region having a sequence set forth as: SEQ ID NO: 89.

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21. The ADC of any one of claims 12 to 20, wherein the antibody or antigen binding fragment binds to cell-surface exposed plectin-1.

22. A method for treating cancer, the method comprising administering to a subject having cancer an effective amount of an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2, and an anti-cancer agent.

23. The method of claim 22, wherein the antibody or antigen binding fragment and the anti-cancer agent are administered together, as a composition of any one of claims 1 to 10 or the ADC of any one of claims 11 to 21.

24. The method of claim 22, wherein the antibody or antigen binding fragment and the anti-cancer agent are administered separately.

25. The method of any one of claims 22 to 24, wherein the cancer is characterized by expression of plectin-1 on the surface of the cancer cell.

26. The method of any one of claims 22 to 25, wherein the cancer is ovarian cancer, esophageal cancer, head and neck squamous cell carcinoma, or pancreatic cancer, optionally wherein the pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC).

27. The method of any one of claims 22 to 26, wherein the subject is a mammal, optionally a human.

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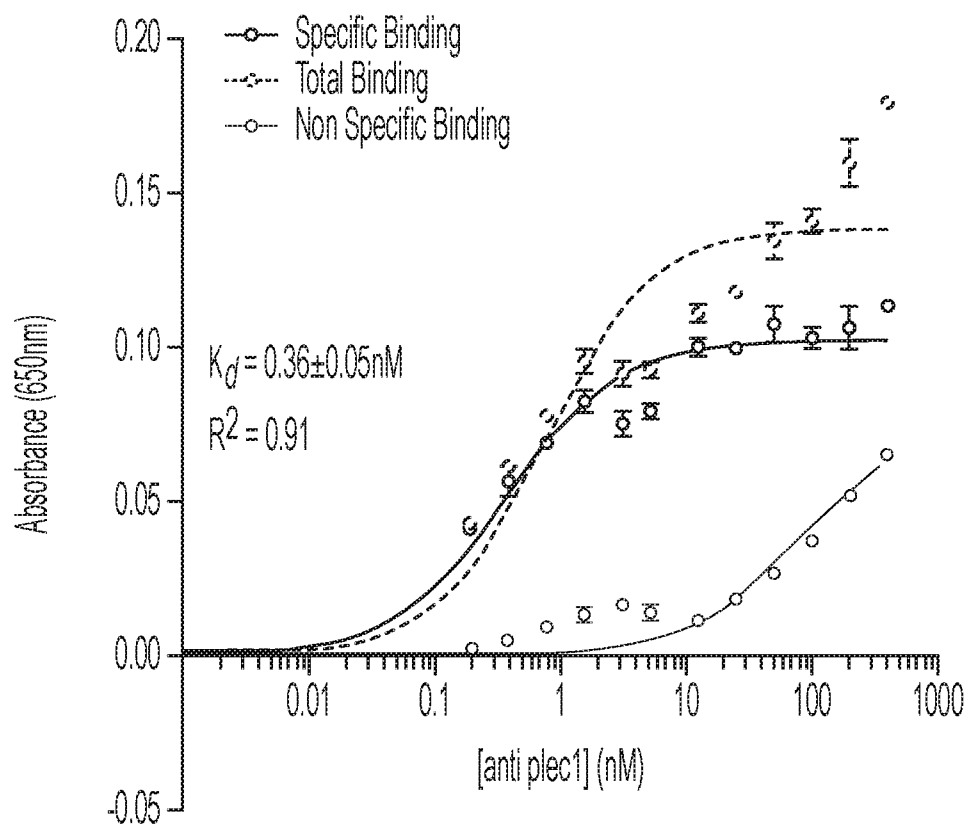


FIG. 1A

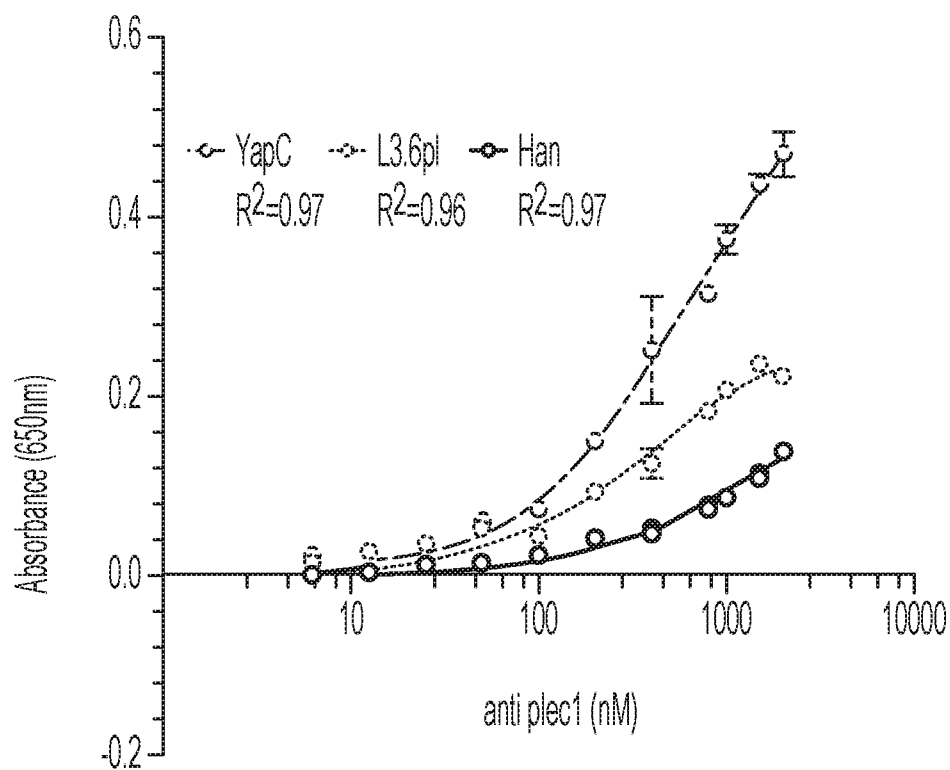


FIG. 1B

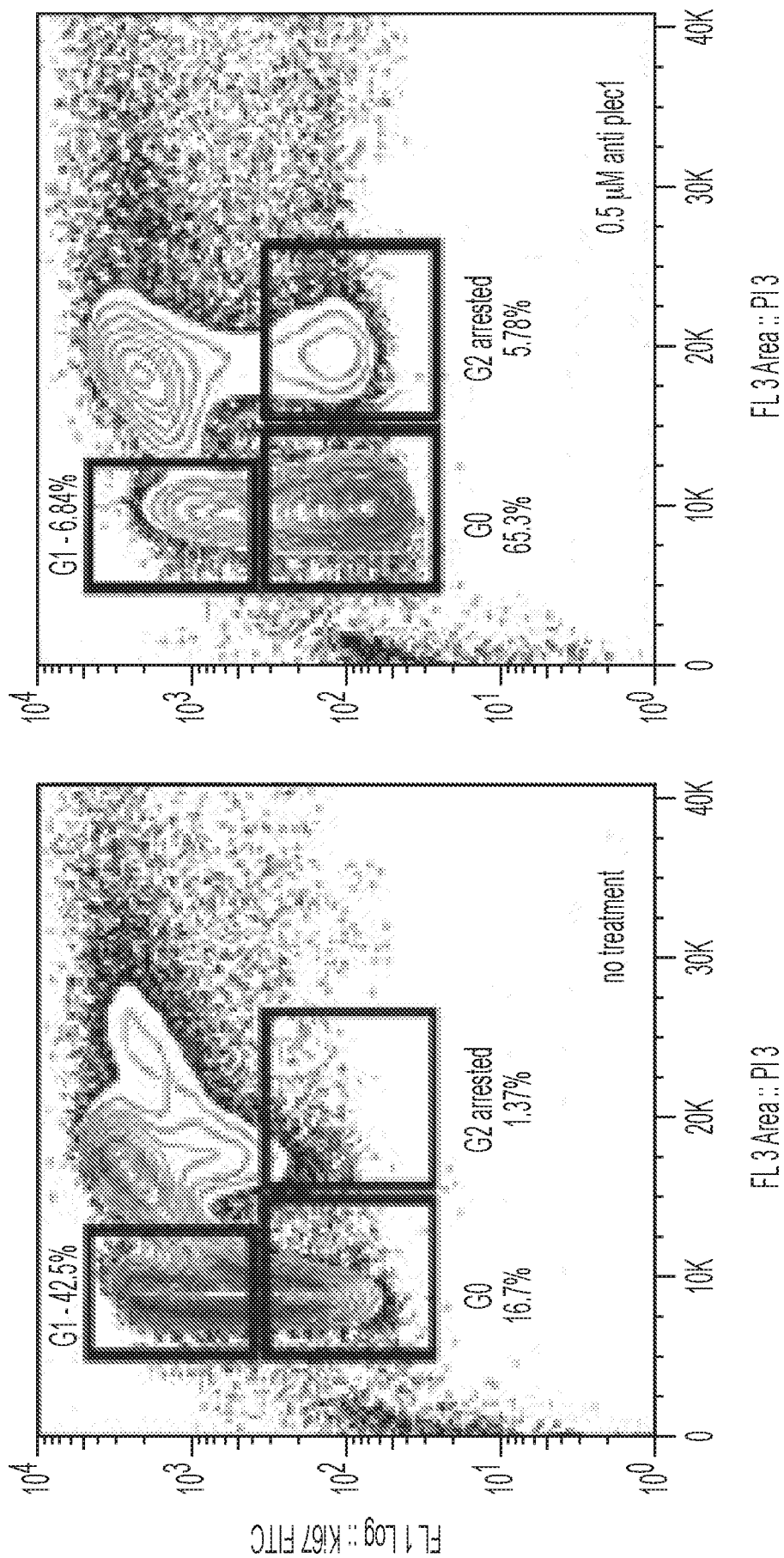


FIG. 2A

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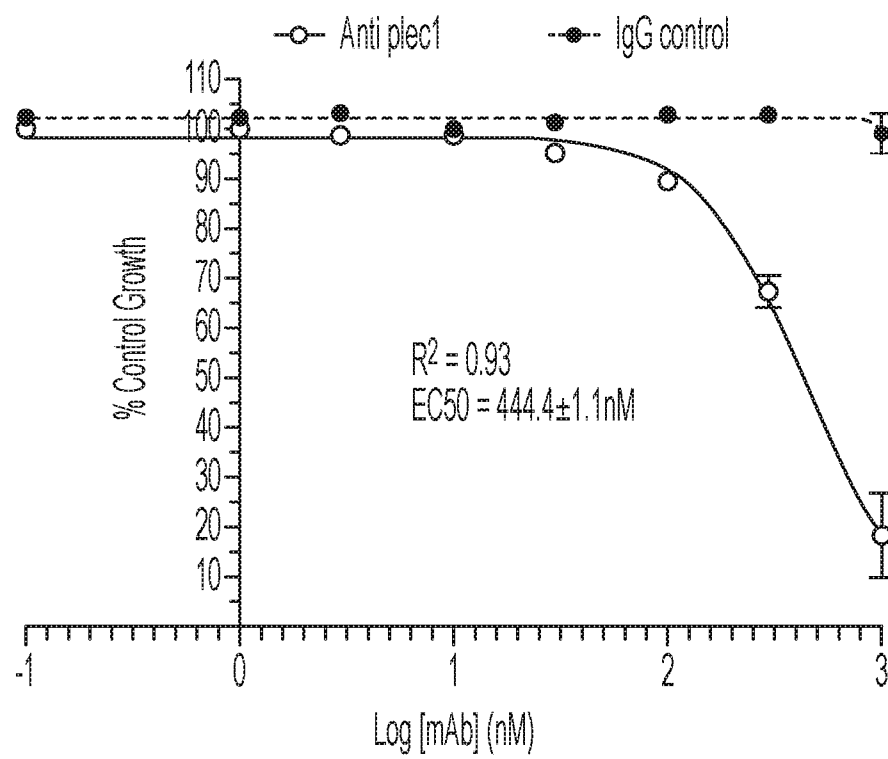


FIG. 2B

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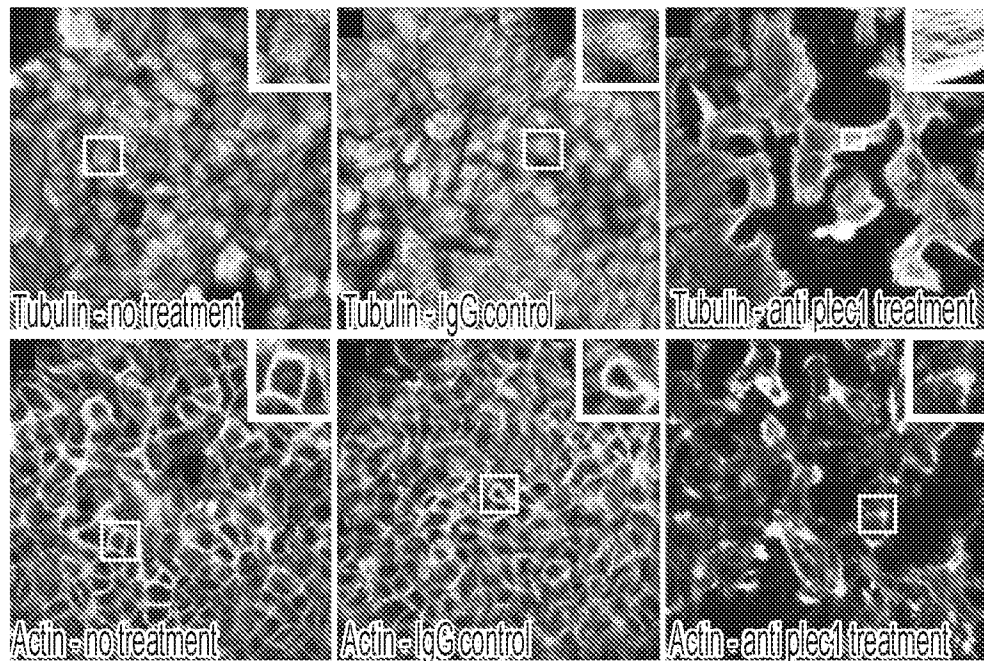


FIG. 2C

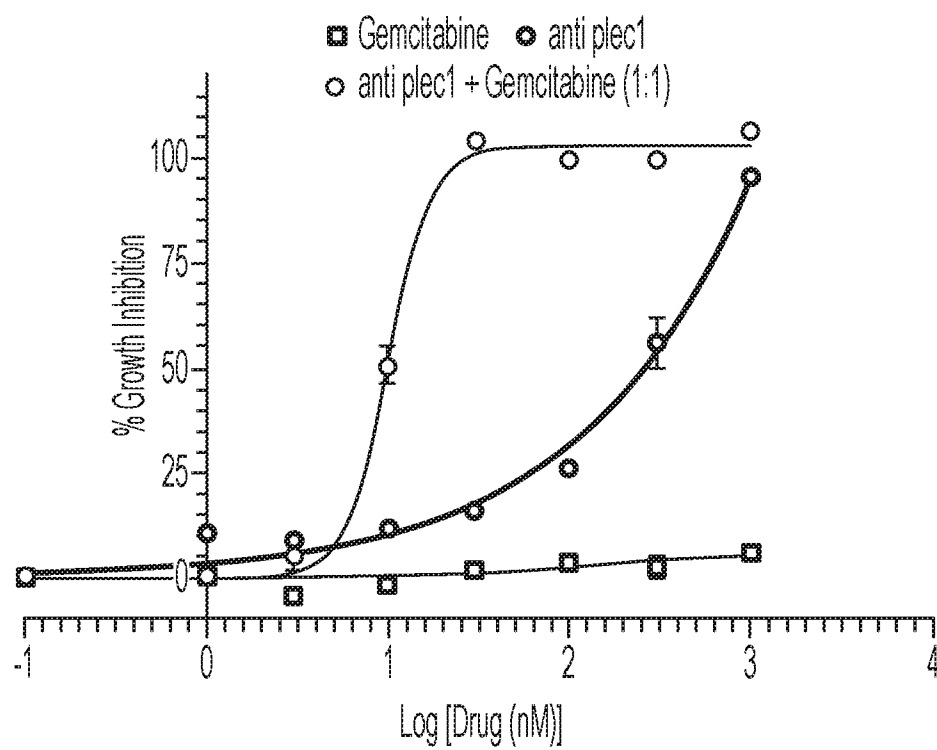


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/55438

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☒ forming part of the international application as filed:
☒ in the form of an Annex C/ST.25 text file.
☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/55438

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 7-10, 15-21, 23, and 25-27
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups I+, claims 1-6, directed to a composition comprising: (i) an antibody that specifically binds to plectin-1 (claim 1), or (i) an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2 (claim 2). The antibody or antigen binding fragment will be searched to the extent that the antibody or antigen binding fragment encompasses wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 23 and a light chain variable region having a sequence set forth as: SEQ ID NO: 45. It is believed that claims 1-2, 3-4(in part), 5/[1-2, 3-4(in part)] encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 23 and a light chain variable region having a sequence set forth as: SEQ ID NO: 45. *****Continued in the extra sheet*****

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-2, 3-4(in part), 5/[1-2, 3-4(in part)], limited to SEQ ID NO 23 and SEQ ID NO: 45 [SEQ ID NO: 2 is a common technical feature]

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/55438

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/00; A61K 39/395; A61K 38/00; A61K 9/14; C12P 21/08; C07K 16/00 (2018.01)

CPC - A61K 2039/505; C07K 2317/24; A61K 39/00; C07K 16/18; C07K 2319/00; A61K 47/48769; A61K 47/48853; C07K 2317/60; C07K 2317/56; C07K 2317/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 2017/0087257 A1 (THE GENERAL HOSPITAL CORPORATOIN) 30 March 2017 (30.03.2017), para [0011], [0018], [0034], [0040], [0041], [0078], [0148], [0166], [0192], [0207], [0235], and [0236]	1-2 ----- 3-5
Y --- A	US 2017/0267719 A1 (COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH et al.) 21 September 2017 (21.09.2017), Abstract, para [0068], [0079], and [0085]	1-2 ----- 3-5
Y --- A	US 2004/0101874 A1 (GHOSH et al.) 27 May 2004 (27.05.2004), pg 52, SEQ ID NO: 1801 (1029 a.a.), the region between amino acid residues 666-1029	2 ----- 3-5
A	US 2015/0299334 A1 (MINERVA BIOTECHNOLOGIES CORPORATION) 22 October 2015 (22.10.2015), para [0027], [0034], and pg 6, col 2, SEQ ID NO: 17	3-5
A	US 2010/0279932 A1 (LEDBETTER et al.) 04 November 2010 (04.11.2010), para [0077], [0649], and SEQ ID NO: 121 (133 a.a.), the region between amino acid residues 21-132	4-5
A	CHENG et al., Plectin deficiency in liver cancer cells promotes cell migration and sensitivity to sorafenib treatment. Cell Adh Migr. 2018 Jan, Vol. 12(1), p. 19-27. Epub 2017 Feb 17. Entire documentation, especially Abstract	1-5
A	SHIN et al., Unexpected gain of function for the scaffolding protein plectin due to mislocalization in pancreatic cancer. Proc Natl Acad Sci U S A. 2013, Vol. 110(48), p. 19414-9. Entire documentation, especially Abstract, and pg 19414, col 2, middle para	1-5
A	PROBY et al., Human Autoantibodies against HD1/Plectin in Paraneoplastic Pemphigus. J Invest Dermatol. 1999, Vol. 112(2), p. 153-6. Entire documentation, especially Abstract	1-5



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 December 2018

Date of mailing of the international search report

24 JAN 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/55438

Continuation of:
Box No III (unity of invention is lacking)

(Continuation of Groups I+) Additional antibody or antigen binding fragment will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibody or antigen binding fragment. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 67 and a light chain variable region having a sequence set forth as: SEQ ID NO: 89 [claims: (1-2), 3-4(in part), 6/((1-2), 3-4(in part))].

Group II, claims 11-14, directed to an antibody-drug-conjugate (ADC).

Group III, claims 22 and 24, directed to a method for treating cancer.

The inventions listed as Groups I+, II-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Feature

Groups I+, II-III are related as a product (Groups I+ or II) and methods of potentially using the product (Group III).

Groups I+ include the special technical feature of wherein the antibody and the anti-cancer agent are not linked, not required by Group II.

Group II includes the special technical feature of an antibody-drug-conjugate (ADC), not required by Groups I+.

Group III includes the special technical feature of treating cancer, not required by Groups I+ and II.

Among Groups I+, each SEQ ID NO represents a structurally different antibody sequence.

Common Technical Features

The inventions of Groups I+, II-III share the technical features of: I) an antibody that specifically binds to plectin-1 exposed on the surface of a cancer cell, and an anti-cancer agent (part of claim 1); and/or II) an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2, and an anti-cancer agent (part of claim 2); and --part of the inventions of Groups I+ further share the technical features of:

-- a composition comprising:

(i) an antibody that specifically binds to plectin-1 exposed on the surface of a cancer cell; and

(ii) an anti-cancer agent,

wherein the antibody and the anticancer agent are not linked (claim 1; which covers the shared technical features I) by Groups I+, II-III); or

--a composition comprising:

(i) an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 2; and

(ii) an anti-cancer agent,

wherein the antibody and the anti-cancer agent are not linked (claim 2; which covers the shared technical features II) by Groups I+, II-III); and further

--wherein the antibody comprises a heavy chain variable region and a light chain variable region (part of claims 3-6).

However, these shared technical features do not represent a contribution over prior art as being obvious over US 2017/0087257 A1 to THE GENERAL HOSPITAL CORPORATION (hereinafter 'GEN_HOSP'), in view of US 2017/0267719 A1 to COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH et al. (hereinafter 'COUNCIL_SCI'); or/and further in view of US 2004/0101874 A1 to GHOSH et al. (hereinafter 'Ghosh') as follows:

GEN_HOSP discloses a composition (para [0040] - 'a pharmaceutical composition') comprising:

(i) an antibody that specifically binds to plectin-1 (para [0040] - 'a pharmaceutical composition comprising a ligand, wherein the ligand binds to plectin-1'; para [0018] - 'plectin-1 binding moiety is the invention provides ligands for a biomarker, wherein the ligand is ... an antibody'; para [0011] - 'plectin-1 ligands ... including a plectin-1 binding moiety, ... the plectin-1 binding moiety is an anti-plectin-1 antibody or antigen-binding fragment thereof')

--exposed on the surface of a cancer cell (para [0078] - 'a binding molecule may reside on a cell surface... binding molecule is a plectin-1 molecule'; para [0166] - 'bind to cell surface antigens on PDAC cells. ...identified plectin-1 as a novel biomarker of PDAC...discovered plectin-1 as a biomarker for pancreatic cancer cells... in the diagnosis... treatment of PDAC in humans'; para [0148] - 'biomarkers of pancreatic ductal adenocarcinoma (PDAC) cell biomarkers ... such as plectin-1'; para [0018] - 'plectin-1 binding moiety is the invention provides ligands for a biomarker, wherein the ligand is ... an antibody'); and

(ii) an anti-cancer agent (para [0040] - 'treating a patient with pancreatic cancer ... providing...a pharmaceutical composition comprising a ligand, wherein the ligand binds to plectin-1... the pharmaceutical composition further comprises a therapeutic agent.... the therapeutic agent is...a toxin, ... a drug', wherein each of 'a toxin, ... a drug' comprising 'an anti-cancer agent', see the quotations that follow; para [0235] - 'provides drugs ... that reduce or eliminate cancer by binding to a cancer biomarker (e.g., plectin)'; para [0236] - 'anticancer drugs'; para [0041] - 'treating a subject who has pancreatic cancer. ... administering a therapeutically effective amount of a pharmaceutical composition including ... a cytotoxic agent, e.g., a toxin or a drug').

*****Continued in the next extra sheet*****

Continuation of:

The previous extra sheet - Box No III (unity of invention is lacking)

GEN_HOSP further discloses wherein the plectin-1 serves as a receptor for targeted cancer therapy (para [0192] - 'kill or ablate cancerous cells, a peptide ligand can be conjugated with a prodrug ... prodrug activator is conjugated with a second peptide ligand, ... that binds to a non-competing site on the same receptor (e.g., plectin-1)'; para [0078] - 'receptor, ... refers to any "binding molecule" ... a cancer cell protein ... a binding molecule may reside on a cell surface ... binding molecule is a plectin-1 molecule'; para [0034] - 'receptor is plectin-1'; para [0207] - 'Concentration ranges of a drug in vitro in which peptide ligand targeting may enhance the ability of a drug to selectively kill cancer cells'; para [0011] - 'plectin-1 ligands ... including a plectin-1 binding moiety, ... the plectin-1 binding moiety is an anti-plectin-1 antibody'; para [0040], quotation as above).

GEN_HOSP does not specifically teach wherein the antibody and the anticancer agent are not linked. COUNCIL_SCI discloses a formulation comprising a Plectin-1 receptor targeting peptide and a therapeutic agent for treating cancer (Abstract - 'a Plectin-1 receptor targeting novel cationic KTLTPK-lipo-peptide, ... a liposomal formulation comprising the cationic KTLTPK-lipo-peptide, ... therapeutic agents and a pharmaceutically acceptable carrier... a method for regressing established pancreatic tumors comprising administering therapeutically effective amount of the liposomal formulation with the therapeutic agents'; para [0068] - 'combating pancreatic cancer'), wherein the Plectin-1 receptor targeting peptide and the therapeutic agent are not linked (para [0068] - 'combating pancreatic cancer by simultaneous applications of both the targeted chemotherapy ... the targeted chemotherapy part of the present combination approach, pancreatic tumor targeting liposomes of KTLTPK-lipo-peptide A is used in delivering the liposomally co-encapsulated curcumin & gemcitabine', wherein 'co-encapsulated' indicating wherein 'the Plectin-1 receptor targeting peptide' - 'KTLTPK-lipo-peptide' and 'the therapeutic agent' - 'curcumin & gemcitabine' are not linked; para [0079] - 'Combination of Curcumin and Gemcitabine Co-Encapsulated in Liposomes of KTLTPK-Lipo-peptide Show Synergistic Effect in Inducing Apoptosis in Pancreatic Tumor Cells'; para [0085] - 'ingredients of liposomal formulation of the present invention for targeted chemotherapy include plectin-1 receptor selective novel lipo-peptide comprising plectin-1 targeting KTLTPK-octa-peptide ... potent therapeutic agents (curcumin and gemcitabine, co-encapsulated within the liposomes of KTLTPK-lipo-peptide)').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of GEN_HOSP and COUNCIL_SCI, to obtain a composition comprising: (i) an antibody that specifically binds to plectin-1 exposed on the surface of a cancer cell; and (ii) an anti-cancer agent, based on the teaching of GEN_HOSP, and further wherein the antibody and the anti-cancer agent are not linked, based on the combination of COUNCIL_SCI and GEN_HOSP, in order to combine methods, antibodies that specifically bind to plectin-1 exposed on the surface of a cancer cell, and technologies available in the art for facilitating obtaining a composition comprising an anti-plectin-1 antibody that can target an anti-cancer agent to a targeted cancer cell without conjugating the anti-cancer agent for treating the targeted cancer with a desired effect with an expected success and without undue experimentation.

Furthermore, GEN_HOSP discloses a composition (para [0040]; quotation as above, this will be applied to the following discussions when the same quotations and explanations are used) comprising:

(i) an antibody or antigen binding fragment that specifically binds an amino acid sequence of plectin-1 (para [0040]; para [0018]; para [0011] - 'plectin-1 ligands ... including a plectin-1 binding moiety, ... the plectin-1 binding moiety is an anti-plectin-1 antibody or antigen-binding fragment thereof', wherein 'the plectin-1 binding moiety is an anti-plectin-1 antibody or antigen-binding fragment thereof' indicating 'an antibody or antigen binding fragment that specifically binds an amino acid sequence of plectin-1'); and

(ii) an anti-cancer agent (para [0040]; para [0235]; para [0236]; para [0041]).

GEN_HOSP further discloses wherein the plectin-1 serves as a receptor for targeted cancer therapy (para [0192]; para [0078]; para [0207]; para [0011]; para [0040]).

GEN_HOSP neither specifically teaches wherein 'the amino acid sequence of plectin-1' is 'an amino acid sequence having at least 85% identity to SEQ ID NO: 2', nor teaches wherein the antibody and the anti-cancer agent are not linked. Ghosh discloses a plectin-1 amino acid sequence (pg 52, SEQ ID NO: 1801, GENE BANK ACC. NO. 14043217 - 'plectin 1, intermediate filament bindi'), which consisting of 1029 amino acid residues, and comprising a region between amino acid residues 666-1029, which is 100% identical to the claimed SEQ ID NO: 2.

Ghosh also does not specifically teach wherein the antibody and the anti-cancer agent are not linked.

COUNCIL_SCI discloses a formulation comprising a Plectin-1 receptor targeting peptide and a therapeutic agent for treating cancer (Abstract; para [0068]), wherein the Plectin-1 receptor targeting peptide and the therapeutic agent are not linked (para [0068]; para [0079]; para [0085]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of GEN_HOSP, Ghosh, and COUNCIL_SCI, to obtain a composition comprising: (i) an antibody or antigen binding fragment that specifically binds an amino acid sequence of plectin-1; and (ii) an anti-cancer agent, based on the teaching of GEN_HOSP, wherein 'the amino acid sequence of plectin-1' is 'an amino acid sequence having at least 85% identity to SEQ ID NO: 2', based on the combination of Ghosh and GEN_HOSP, and further wherein the antibody and the anti-cancer agent are not linked, based on the combination of COUNCIL_SCI, Ghosh, and GEN_HOSP, in order to combine methods, antibodies that specifically bind to an amino acid sequence of plectin-1, the amino acid sequences of plectin-1, and technologies available in the art for facilitating obtaining a composition comprising an anti-plectin-1 antibody that can target an anti-cancer agent to a targeted cancer cell without conjugating the anti-cancer agent for treating the targeted cancer with a desired effect with an expected success and without undue experimentation.

Although the said combination does not specifically teach wherein the antibody comprises a heavy chain variable region and a light chain variable region, this limitation is determined by the inherent property of an antibody, as evident by Wikipedia_Antibody (Heavy chain - 'Each heavy chain has two regions, the constant region and the variable region'; Light Chain - 'A light chain has two successive domains: one constant domain and one variable domain'; The reference is not provided, as it belongs to common knowledge).

Without a shared special technical feature, the inventions lack unity with one another.

Groups I+, II-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Continuation of item 4: Claims 7-10, 15-21, 23, and 25-27 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.